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International Medical Digest

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General Medicine

The Abuse of Bed Rest in the Treatment of Myocardial Infarction — IRVIN, C. WARREN, JR. AND BURGESS, ALEXANDER M., JR. — *New England Journal of Medicine*, 243: 486 (September 28) 1950.

"There is no statistical evidence that bed rest, or even markedly restricted activity over a prolonged period, advantageously affects either the course or the later sequelae of myocardial infarction. . . . Bed rest has long been the sine qua non in the treatment of myocardial infarction, and periods of four weeks or more as a minimum are advised by most textbooks and authorities."

"The important advantages ascribed to bed rest are the avoidance of cerebral anoxia during shock, prevention of sudden death and preservation of myocardial function. The first is an immediate protection to the patient whose circulatory collapse briefly necessitates a recumbent or head-down position."

"The disadvantages of recumbency are many. The circulation to the basilar part of the lungs is poor; atelectasis, hypostatic pneumonia and constipation are common." One writer suggests that congestive failure may get worse in the recumbent position, and one writer considers the sitting position more favorable for patients with angina pectoris. "The development of phlebothrombosis and subsequent embolization is much higher, and this fact should not be lost sight of even though Dicumarol has done much in preventing fatal emboli." One writer recently working with normal young human volunteers subjected to prolonged bed rest, found the exercise tolerance, as measured by the Master and Schneider tests, markedly decreased—requiring many weeks to return to normal. "He noted many other disadvantages of prolonged bed rest, including abnormal nitrogen and calcium metabolism and deterioration in the mechanisms essential for adequate circulation in the erect position as indicated by an increased tendency to faint in tilt-table tests: 'Experiments indicated that the legs were the principal site of changes responsible for this deterioration and suggested that increased venous engorgement, increased extravascular fluid, capillary fragility and impaired venous or muscle tone play a role.'

"Finally, the psychogenic sequelae are too easily overlooked. With some physicians who are particularly adept at handling this problem, and who are constantly aware of it, the number of patients so harmed may be relatively few. The great majority, however, do not escape so easily. It is with alarming frequency that one sees in the clinic, patients who have had myocardial infarction but who have been pitifully inactive because of symptoms brought on by fear rather than heart disease. In the increasingly older population the economic factors, even if the emotional ones could be disregarded, are serious enough to make further investigation imperative.

"In summary, then, there are two main aims in the treatment of myocardial infarction. The first is the immediate saving of the patient's life, and the second is to prepare him for further living. The latter has probably often been neglected in the earnest desire to accomplish the first. . . . The greatest fault has probably been not only in the length of bed rest but also in the rigid routine that is practiced. In most cases this includes four weeks of absolute, or nearly absolute, bed rest followed by varying lengths of inactivity so that rarely is the patient without residual symptoms returned to normal activity in less than three months. It is ridiculous for patients, who have not even been allowed to feed themselves to perform the dangerous Valsalva experiment upon the bedpan daily, owing to their unaccustomed constipation. Actually, it is impossible to

accomplish to even a reasonable degree what is desired by the orders of 'complete bed rest' or 'coronary precautions.' This is clearly shown by Stead's experiments, in which emotions are shown markedly to increase cardiac output—perhaps more frequently in these patients forced into undesired recumbency than would occur with gradually increased, intelligently guided activity.

"It is important and lamentable that prolonged bed rest has become such a recognized part of the treatment of myocardial infarction in the eyes of both the patient and the physician. This makes it difficult for those who desire to recommend earlier ambulation since an unfortunate incident or coincidence may damage the reputation of the physician. In truth, many honest physicians have admitted that this is the prime reason for keeping their patients in bed."

It is the writers' considered opinion that routine prolonged bed rest in myocardial infarction is not only unnecessary but also potentially harmful to the mental and physical well-being of the patients. "Two weeks in bed, with reasonable, carefully explained restrictions, and possibly bedside toilet privileges, would be all that is necessary in the majority of cases. Even during this period some gradually increasing activity might be begun. After this, in the absence of contradictory symptoms and signs, patients should be gradually and progressively allowed to walk until at the end of four weeks from the onset they have regained some of their previous exercise tolerance and are prepared to leave the hospital on light activity. By this method not only would the patient be able to return to gainful occupation sooner but perhaps some of the physical and mental disturbances of bed rest would be circumvented. Obviously, there will be a certain number of cases in which extensive infarction would require modification of this procedure.

"The foregoing recommendations do not appear to be in conflict with presently known facts, but it must be emphasized that applicable statistically valid facts are few. It is to be hoped that the treatment of myocardial infarction may one day rest on the results of purposeful clinical study, rather than mere reasoned opinion." In any case, although the writers believe that bed rest in most cases can be advantageously and safely shortened, no blanket recommendation applicable to all patients can or should be offered.

Streptomycin and Neomycin. An Antibiotic Approach to Tuberculosis — WAKSMAN, SELMAN A. — *British Medical Journal*, 2: 595 (September 9) 1950.

"The first results obtained with streptomycin proved to be encouraging. It is now barely five years since the first clinical cases were reported and since the first attempt was made to manufacture streptomycin in sufficient amounts for large scale clinical evaluation; a wealth of information which permits certain broad generalizations has already accumulated.

"In general, the laboratory demonstrations of the effectiveness of streptomycin in vitro, followed by the experimental proof of its usefulness in experimental animals, were fully substantiated by numerous clinical investigations. The large scale studies conducted in England by the Medical Research Council, and in the United States by the Veterans Administration (Council on Pharmacy and Chemistry, 1950) and the American Trudeau Society (1950), produced adequate evidence that an agent for the treatment of tuberculosis was finally available. Although many hundreds of drugs were previously reported to control the tubercle bacillus in the culture tube, none were able to do so in the animal body. Many drugs that have been effective against the infection in animals were found to be impracticable against the same disease in man. In the case of streptomycin the analogy from laboratory to animal to man held well. It was only in the clinic, however, that investigators finally learned of the potentialities of streptomycin, on the one hand, and of its limitations and dangers on the other."

"In submitting its report to the Council on Pharmacy and Chemistry (1950), the committee in charge of the work at the Veterans Administration emphasized the importance of combining surgical procedures with chemotherapy. The use of daily doses of 1 Gm. or less has decidedly reduced the incidence of toxic manifestations. The development of resistant microorgan-

isms was delayed, especially by the combined administration with paraamino salicylic acid.

"The American Trudeau Society Committee (1950) recommended for adults 1 Gm. of streptomycin, administered in a single dose intramuscularly, or 1 or 2 Gm. of dihydrostreptomycin in one or two injections. In miliary tuberculosis and tuberculous meningitis in adults, 2 or 3 Gm. a day, given intramuscularly in two or three doses of 1 Gm. each, was recommended. To overcome the emergence of streptomycin-resistant organisms, it has been recommended that streptomycin be administered at greater intervals, as 1 Gm. every third day or twice a week, or that its daily administration be combined with paraamino salicylic acid."

Since they were first recognized, meningeal and acute miliary tuberculosis have involved a mortality rate of 100 per cent. "The time between onset of disease and death was measured in weeks, especially in meningitis. These two forms provided, therefore, an ideal testing ground for the efficacy of streptomycin. It has fully justified itself. Its ability to suppress or destroy the tubercle bacillus was demonstrated. The effectiveness of streptomycin is now generally agreed on by investigators in the United States of America, in England, and in other European countries. In one series of 100 patients with proved diagnoses, 24 were alive between 14 and 26 months after treatment had been instituted."

"Pulmonary tuberculosis is commonly considered, both in incidence and in the number of lives it takes, as one of the most serious forms. Since 1900, the mortality rate of tuberculosis has been reduced in the United States of America to 20 per cent of its previous rate. In 1942, however, 52,000 deaths were still ascribed to tuberculosis, and of these, 92 per cent were due to pulmonary disease. . . . The prolongation of life in patients with meningeal and miliary tuberculosis was ample evidence that streptomycin had a definite effect on tuberculosis. The chronic nature of pulmonary tuberculosis suggests that years will pass before the effectiveness of streptomycin can be evaluated by its effect on the mortality rate.

"In the relatively short period since its introduction, however, there has been substantial agreement among investigators that certain immediate results may be expected from its use. The question of toxicity and the development of bacterial resistance were the two controlling factors in establishing the most desirable duration of treatment. Originally a period of 120 days was selected. To lessen the incidence of resistance a decrease in duration of treatment has often been recommended. A reduction in efficacy did not seem to accompany a reduction in duration of treatment to 60 days. A further reduction to 42 days appeared to decrease the efficacy of streptomycin but certainly did not destroy it. The tendency over the last two years has been to reduce the daily dosage of streptomycin from 2 Gm. to 1 Gm. or even to 0.5 Gm. and to reduce the period of treatment from 120 days to 60 days or even less. The first is an attempt to avoid toxicity, and the second to reduce the incidence of resistance."

"The ability of streptomycin to produce healing of tuberculous lesions of mucous and serous membranes, extending to lesions which involve the skin and its underlying tissues, was reported to be most remarkable. Prior to its use, cutaneous sinuses usually continued to drain for years. Their surgical treatment and closure were rarely possible. When treated with even small doses of streptomycin most sinuses were found to heal readily. The effect is so striking that it was not even considered necessary to have untreated controls. In the first clinical report of streptomycin therapy all sinuses in 3 patients healed during treatment."

Among the most important problems involved in the use of streptomycin in tuberculosis is the development of resistance. "This is brought out in a study of the effect of different concentrations of streptomycin upon the rate of growth of *Mycobacterium tuberculosis*. . . . Whether by intermittent administration, or by combination of streptomycin with sulphones or paraamino salicylic acid, or with some other tuberculostatic agent, it was found possible to delay the onset of streptomycin resistance. By shortening the course of therapy for pulmonary tuberculosis to four or six weeks the incidence of resistant

strains is diminished. There is considerable variation in the development of drug-resistant strains in the study of a large group of patients. Those who have definite pulmonary cavitation are more likely to produce resistant cultures than are those without cavitation. Patients who start treatment with a high bacillary count in the sputum show a greater tendency to yield drug-resistant cultures during streptomycin therapy than those with few organisms in the sputum. *Myco. tuberculosis* lodged in the central nervous system becomes resistant less readily than it does in the lungs.

"The possibility of utilizing a combination of two antimycobacterial agents appears, for the present at least, to provide an answer to the problem of development of resistance. . . . Another answer may be found in the search for new antibiotics." This may be accomplished by the use of neomycin.

"Neomycin is more active than streptomycin against both the saprophytic Mycobacterium 607 and the human and animal pathogenic strains of *Myco. tuberculosis*.

"Neomycin is as active against the streptomycin-resistant strains of the above organisms as against the sensitive ones.

"Neomycin favours to a far less degree than does streptomycin the development of resistant strains of Mycobacteria; it is true that on prolonged serial transfer of large numbers of cells a considerable increase in resistance may be obtained, but the rate of increase is much slower than in the case of streptomycin.

"Neomycin is characterized by a relatively low toxicity in animals and has a high therapeutic index."

"In human tuberculosis there is an immediate reaction consisting of lowering of the fever and a feeling of well-being." The writer has not seen toxic reactions with low doses. "In 2 patients there was an increase of the N.P.N. and of the sedimentation rate, which disappeared when the drug was stopped. In some cases, however, definite evidence of a nephrotoxic and ototoxic action was reported."

The possibility of combined action of neomycin and streptomycin or another antimicrobial agent is receiving much consideration.

Clinical Studies with ACTH and Cortisone in Renal Disease — THORN, GEORGE W., MERRILL, JOHN P., SMITH, STEPHEN, III, ROCHE, MARCEL AND FRAWLEY, THOMAS F. — *Archives of Internal Medicine*, 86: 319 (September) 1950.

"The devastating effects of glomerular nephritis and the considerable disability induced by this disease are well known. The fact that nephritis has a predilection for children and young adults serves as an additional stimulus to the search for a means of controlling the disease. To date, therapy is limited to procedures which ameliorate the metabolic abnormalities secondary to renal failure or attempts to reduce the incidence of intercurrent infections." The dramatic effect which pituitary adrenocorticotropic hormone (ACTH) and cortisone exert on the course of a wide variety of systemic diseases of unknown origin, especially those in which an antigen-antibody type of reaction is believed to play an important etiologic role, stimulated the writers to investigate the possible beneficial effect of these hormones in patients with glomerular nephritis. "Furthermore, earlier studies indicating an apparent competitive inhibition of cortisone on excessive sodium retention induced by desoxycorticosterone naturally suggested an investigation of these phenomena in patients with nephrotic edema.

"Sporadic attempts to modify the course of subacute nephritis met with little success initially. It was clearly evident that the response of patients with glomerular nephritis was far different from that observed in patients with rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and certain allergic disorders."

In 2 of the writers' patients there was an increase in nitrogen retention, and in 1 a decided elevation of blood pressure occurred in spite of remarkable clearing of the concomitant skin lesions. "In 1 patient with subacute nephritis the appearance of hematuria during ACTH therapy was disappointing, while in 4 others an increase in hematuria following omission of the drug may have attested to some beneficial effect. In 2 patients definite diminution in the skin reaction to the hemolytic streptococcus occurred, in spite

of indefinite effect on the renal disease. These observations stimulate speculation concerning the possible difference in the role of hyperimmune reaction and inflammatory response in nephritis and other 'collagen diseases.' "

"The role of ACTH and cortisone in decreasing this inflammatory response and the fibroblastic reaction has been pointed out. It is possible that this may be of benefit in the early stages of acute nephritis, although its only clinical manifestation is a disappearance of grossly bloody urine without affecting microscopic hematuria. That such an effect may possibly be of benefit in the anuria of acute nephritis or in the prevention of subsequent fibrosis and destruction of glomeruli with functional impairment must await careful study of a far greater series of cases.

"The mechanism by which edema fluid accumulates in patients with nephrotic syndrome is poorly understood. Although proteinuria and hypoproteinemia are contributory factors, they are by no means the whole story. It is well known that a spontaneous diuresis may occur without demonstrable change in serum protein level or in the degree of proteinuria. . . . It is an attractive hypothesis to consider that many of the nonspecific mechanisms concerned with the initiation of diuresis in patients with the nephrotic syndrome may in part, at least, involve the pituitary-adrenal system and may in fact be simulated by the administration of ACTH.

"The mechanism by which the administration of ACTH and the increased release of adrenal steroids initiates a diuresis is also not yet understood. The simplest case is that in which ACTH is given for five to seven days with some sodium and water retention, followed by a prompt diuresis 24 to 48 hours after ACTH is withdrawn. At first thought this might be considered to be due to a temporary state of adrenocortical inactivity (insufficiency) following excessive stimulation of the cortex with relatively large doses of ACTH. This hypothesis is supported by the fact that no appreciable increase in potassium excretion is observed despite the magnitude of the diuresis and by the fact that the eosinophil content returns rapidly to normal or supranormal level. Changes in 17-ketosteroid excretion are difficult to interpret because of the increased urine volume which so characteristically accompanies a diuresis.

"That this mechanism is not the whole story is suggested by the fact that cortisone treatment in a dosage which has been shown to be a potent inhibitor of endogenous adrenal secretion is not followed by as significant a diuresis as occurs following the administration of large doses of ACTH. Furthermore, during the sodium diuresis which follows ACTH withdrawal, a reduced sensitivity to desoxycorticosterone administration occurs, in contrast to the greatly increased sensitivity observed in patients with Addison's disease. Thus, very large doses of desoxycorticosterone acetate (20 to 40 mg.) do not elicit the extremely low urinary sodium values observed in patients with uncomplicated adrenocortical insufficiency similarly treated. This reduced effectiveness is also true of posterior pituitary hormone administered every two to three hours round-the-clock." These facts suggest tubular "fatigue" or decreased responsiveness to hormone action as an important adjunct in explaining the diuresis which follows withdrawal of ACTH.

"The delay in the onset of diuresis (24 hours) after ACTH is withdrawn supports the importance of relative adrenal insufficiency in contrast to 'tubular' fatigue or refractiveness since a rapid regression in adrenocortical steroid elaboration follows the withdrawal of ACTH. The combination of tubular 'fatigue' and relative adrenal insufficiency would, of course, lead to tremendous salt and water excretion in patients with increased plasma volume and large quantities of extracellular fluid available for excretion. In patients . . . . in whom evidence of excess extracellular fluid had disappeared, such a diuresis did not occur, possibly because of the inavailability of excess extracellular fluid and electrolyte."

"Certainly the more complex situation; namely, the sodium and water diuresis which occurs while patients are continuing to receive ACTH in large doses with all indications of excellent adrenocortical activation, cannot be attributed to adrenocortical insufficiency. Here one must postulate renal tubular 'fatigue' or the competitive effect of cortisone-like steroids on the action of desoxycorticosterone-like

steroids, as well as the possible effect of cortisone-like steroids on posterior pituitary secretion and hormonal action. It is also possible that the increased glomerular filtration function which has been demonstrated in patients treated with ACTH may be an important factor in conjunction with the aforementioned mechanisms. It is obvious, however, that adrenocortical insufficiency cannot be evoked as a possible explanation of the sodium diuresis in the presence of greatly increased adrenal steroid secretion during ACTH therapy, unless quantitative changes in the type of steroid elaborated (i.e., 11-desoxycorticosterone, 11-17-oxysteroid) are postulated."

The writers are inclined to believe that the diuresis of sodium and water which occurs in patients with nephrotic syndrome during ACTH treatment is accounted for by (1) renal "tubular fatigue" with reduced sensitivity to adrenal sodium-retaining hormone as a consequence of prolonged high level of 11-17-oxysteroid secretion and/or competitive action of 17-oxysteroids on 11-desoxy-like steroids as a result of a qualitative change in the ratio of steroids secreted by the adrenal cortex under ACTH administration, the (2) increased glomerular filtration fraction during ACTH therapy aided by the tremendous excess of extracellular fluid and electrolyte available for excretion and (3) the enhancement of these effects by temporary adrenocortical insufficiency following the withdrawal of ACTH or cortisone therapy.

"Finally, the persistence of diuresis and the disappearance of protein in the urine, when it occurs following ACTH administration, involve mechanisms of repair at present poorly understood but aided by the reduction in over-all tissue edema."

"There was no conclusive evidence in the small series of patients comprising this study that ACTH and cortisone exert any beneficial effect on the over-all course of acute, subacute and chronic nephritis.

"Metabolic studies carried out in patients with nephrosis treated with ACTH and cortisone revealed differences in the response of respiratory quotient, thyroid function, cholesterol and phospholipid levels from the response under similar conditions in normal persons and in patients with Addison's disease."

Subacute Bacterial Endocarditis — HUNTER, THOMAS H. — *Journal of Missouri State Medical Association,* 47: 661 (September) 1950.

"One of the most dramatic therapeutic results of the introduction of penicillin and the newer antibiotics has been the cure of bacterial endocarditis. . . . Many patients are still dying of bacterial endocarditis unnecessarily, and some of the reasons for this are quite apparent:

"1. Failure of physicians to establish the diagnosis early.

"2. The tendency to treat all 'fevers' blindly with penicillin or sulfonamides (in doses that suppress but do not cure this infection).

"3. When the proper diagnosis is made, failure to detect resistant infections because the antibiotic sensitivity of the causative agent is not determined.

"4. Therapy which is not sufficiently intensive and continuously maintained.

"5. Ignorance of physicians, dentists and patients with valvular heart disease as to the need for prophylaxis with penicillin at the time of tooth extraction, cystoscopy and other operations in infected fields."

"Bacterial endocarditis occurs almost always in patients with previous valvular or congenital heart disease. By far the most common predisposing lesion is rheumatic heart disease and, consequently, the mitral and aortic valves are most often affected. Bacteria, which enter the blood stream from infected teeth, urinary tract, nasopharynx, and probably from other sources as well, land on the damaged valve where they grow embedded in fibrin and necrotic valve substance producing the 'vegetations' of bacterial endocarditis. Bits of vegetations breaking off are responsible for the embolic lesions so characteristic of this disease."

"The importance of early diagnosis cannot be too strongly emphasized, and physicians must educate themselves to think of bacterial endocarditis in any patient with valvular heart disease who runs an unexplained fever for more than a few days. In such cases multiple blood cultures should be taken even though other signs and symptoms are absent.

"Other findings which are common but not necessarily present include: petechiae,

a palpable spleen, clubbing of the fingers, joint pains, tachycardia, changing heart murmurs, elevated sedimentation rate and microscopic hematuria. Osler's nodes, which are tender pea-sized nodules appearing in the pads of the fingers and toes and subsiding in a week or so, are practically diagnostic of the disease. Emboli to cerebral vessels cause a variety of neurologic abnormalities, some transitory and some permanent. In elderly patients particularly, attention may not be especially drawn to the heart. The murmurs are often unimpressive at first and constitutional symptoms may predominate leading to a suspicion of malignant disease, tuberculosis and other chronic infections. Kidney involvement may be so prominent as to suggest a primary diagnosis of nephritis." In short, the clinical manifestations are so protean that the differential diagnosis is endless, and all patients with fever and heart murmurs should have blood cultures taken.

"The finding of several positive blood cultures constitutes the only final means of clinching the diagnosis. Although transient bacteremia due to infected teeth is common, repeated recovery of nonhemolytic streptococci from the blood is almost never found except in subacute bacterial endocarditis. In this disease, positive blood cultures can be obtained in more than 90 per cent of cases sooner or later, but in a few instances in which, on other clinical grounds the diagnosis seems unavoidable, the cultures may be sterile for long periods of time—especially after therapy which has suppressed but not eradicated the infection. In this situation also the organisms may grow slowly and not be detectable in culture flasks until after three weeks incubation. It is therefore urged that at least five or six blood cultures be taken before treatment is started and that they be incubated for three weeks before being discarded as negative. If institution of therapy seems urgent, cultures can be taken at hourly intervals if necessary and thus therapy need be delayed but a short time."

"The first patient successfully treated with penicillin has now been followed for more than seven years and is doing well. By now many hundreds have been cured, but no single regimen has emerged which can be recommended with confidence for every case. Furthermore, the dosage of penicillin advocated for the usual case due to a penicillin-sensitive organism has crept up and up because there continues to be a small proportion of failures under any regimen. The failures become fewer, however, as the daily dose and duration of treatment increase. Certain general principles related to therapy are pretty well established:

"1. Anticoagulants are not indicated.

"2. Sulfonamides are of little value.

"3. The optimal duration of a course of therapy is probably from four to six weeks.

"4. Daily doses of 2,000,000 units of penicillin are recommended for patients whose infecting organism is sensitive to penicillin (inhibited in vitro by 0.1 unit or cc. or less).

"5. The safest method of administering penicillin is intramuscularly every three hours day and night.

"Patients whose organism is more resistant to penicillin, or who prove refractory to this therapy need heroic treatment, but can still usually be cured. No rule of thumb regimen can be outlined for these cases except to say that good results have been obtained using large doses of penicillin 10,000,000 units a day or more, plus streptomycin in doses of 2 to 3 Gm. daily. It may eventually turn out that aureomycin or chloramphenicol will be more satisfactory than streptomycin as adjuncts, but experience with these newer antibiotics in bacterial endocarditis is still limited. Treatment of resistant cases must still be highly individualized and guided largely by the sensitivity of the infecting organism to the available antibiotics singly and in combinations, also taking into account, of course, the patient's response to therapy.

"The appraisal of a patient's response to treatment often is exceedingly difficult. Although many show a prompt subsidence of all clinical signs of active infection within a few days, some continue to have low grade fever, occasional embolic phenomena and other disturbing features throughout treatment even though their subsequent course is satisfactory. If blood cultures remain positive for more than a few days in the face of therapy, it is strong evidence that treatment is grossly inadequate. The

dose of antibiotics necessary for clearing the blood stream is far smaller than the curative dose; hence one cannot accept an apparent clinical response with blood cultures becoming negative as evidence that treatment is necessarily adequate. Thus one has to recognize the unpleasant fact that clinical evidence alone may be quite misleading in the appraisal of a patient's status. For this reason one needs information concerning the sensitivity of the infecting organism to antibiotics because, even with this added help, it may still be difficult to judge whether or not a patient is being cured while therapy is in progress.

"In general it is not advisable to continue a course of therapy beyond six weeks because if the infection is not controlled by that time, it is unlikely that further prolongation of treatment at the same dosage level will effect a cure. If after six weeks the patient's condition is uncertain, it is better to stop treatment altogether and be prepared to institute a new and more intensive course if the patient should relapse. Relapses rarely occur later than one month after treatment is stopped, and most of them are evident within two weeks."

"The infection can be cured in more than 90 per cent of cases, if treatment is intensive, and controlled by careful bacteriologic studies. The deaths which occur in spite of the best available therapy are mostly due to cardiac failure and cerebral accidents, either from emboli or ruptured mycotic aneurysms. These latter complications probably can never be avoided completely, but they can certainly be reduced by early diagnosis and treatment. The rapidity with which valvular damage progresses varies greatly from 1 case to another depending upon the site of the vegetations and the invasiveness of the bacteria causing the infection. Lesions of the aortic valve appear to result in serious impairment of cardiac function most frequently."

"Approximately 25 per cent of patients with bacterial endocarditis give a history of tooth extraction preceding the onset of the disease. A significant number of infections also follow instrumentation of the nasopharynx or genitourinary tract—such procedures as tonsillectomy, sinus operations, cystoscopy, curettage of the uterus and even normal delivery. While it does not seem possible to prevent bacteremia completely at the time of these procedures, there is evidence that bacterial endocarditis can be prevented in susceptible patients by sufficiently intensive antibiotic prophylaxis. It is the doctor's responsibility to educate all patients with valvular or congenital heart disease as to the need for such prophylaxis, and they should be warned never to allow operations to be performed without telling the dentist or surgeon of the instructions they have had. What constitutes the best regimen for prophylaxis is not yet known with certainty, but no cases of bacterial endocarditis have been reported following tooth extractions in patients receiving penicillin in doses of 100,000 units every 3 hours intramuscularly starting at least 6 hours before operation and continued for at least 48 hours. In patients who cannot be hospitalized, procaine penicillin 500,000 units twice daily for the same period is recommended. It seems probable that aureomycin will be useful in prophylaxis not only because of its wide antibacterial spectrum, covering almost all of the organisms both gram-positive and gram-negative which may commonly enter the blood stream, but also because it can be given by mouth. Sulfadiazine, however, has not proved adequate, and several cases of bacterial endocarditis have developed in the face of treatment with full doses of this drug."

Therapeutic Experiences with Subacute Bacterial Endocarditis with Special Reference to the Failures — LITTMANN, DAVID AND SCHAAF, ROYAL S. — *New England Journal of Medicine*, 243: 248 (August 17) 1950.

Recently, the authors reviewed the therapeutic results in subacute bacterial endocarditis at a general hospital and a veterans administration hospital for the years 1947-1949. They were impressed by the increasing infrequency of the disease but also by the unexpectedly high death rate despite what by present standards constituted adequate, and in many cases, more than adequate treatment. "By adequate treatment is meant the use of such quantities of the appropriate antibacterial

agent or agents as are indicated after identification of the organism and determination of its sensitivity to available antibiotics. In practice, this amounted to the administration of from 1,000,000 to 30,000,000 units of penicillin a day for 30 to 60 days. Most patients received 1,000,000 or 2,000,000 units per day (by intermittent intramuscular injection) for 30 days, although 500,000 units a day is probably sufficient in most cases. When no organism could be demonstrated the dosage was generally about 2,500,000 units a day for a month. Streptomycin and, more recently, aureomycin were employed in a few cases. Anticoagulants were not used.

"The dosage levels were greater and the variety of drugs employed superior to those available during the 1944-1946 period. In spite of this, the recovery rate in 37 adequately treated patients with subacute bacterial endocarditis was only 62 per cent, in contrast to 76 per cent in the earlier period."

In the years 1947-1949 at the general hospital there were 38 patients with bacterial endocarditis. "Of these, 6 were acute cases, all of which were fatal. Notwithstanding better diagnostic and therapeutic methods and occasionally reported cures, acute bacterial endocarditis remains an exceedingly serious disease. Enormous quantities of antibiotics were administered in several cases without significantly influencing the course of the illness. As this paper is primarily concerned with endocarditis lenta these cases will not be further considered. Of the remaining 32 cases of bacterial endocarditis 5 were discovered at autopsy or immediately ante mortem and too late for any significant therapy. Two of these were marantic or terminal complications of other fatal illnesses. The other 3 patients had outright subacute bacterial endocarditis and died untreated because the diagnosis was overlooked. These 5 patients are not being considered with the treated cases but are included in the determination of gross incidence. Of the original 38 cases of bacterial endocarditis, therefore, 30 were considered to be clinical subacute bacterial endocarditis. These were collected out of admissions totaling 50,666, an incidence of 0.59:1,000 admissions. During the previous three year period at the same institution there were 51 similar cases out of 46,601 admissions, an incidence of 1.12:1,000." It appears, therefore, that at the general hospital the incidence of subacute endocarditis has diminished by almost half.

During the same three year period at the veterans administration hospital there were 10 patients with subacute endocarditis. "All were adequately treated according to the foregoing definition, and of these, 6 recovered." These cases have been combined with those from the general hospital for the entire six year period. "Altogether there were 52 recoveries and, despite adequate treatment, 23 deaths. The failures have been combined for purposes of analysis and for comparison with the cases in which the patients recovered."

"Age.—There was a striking similarity in the mean age of the patients who recovered as compared to those who died, 40 years in the former and 40.6 in the latter. The youngest patient who recovered was 3½, and the oldest 73 years old. The youngest patient who died was 17, and the oldest 67. Age, apparently, was unrelated to the eventual outcome of the disease.

"Sex.—There was no significant difference in sex distribution between the two groups.

"Duration of Illness Before Recognition.—Delay in diagnosis did not often make the difference between recovery and failure. In the cases in which it did, however, it was of vital importance. In the 3 patients mentioned earlier the diagnosis was not made before death or too late in the course of the disease for adequate therapy to be instituted. In the treated patients the average duration of symptoms before therapy was 11.6 weeks in those who died as against 10.7 in the cured cases. In a patient who recovered, 9 months elapsed before treatment was begun. In a fatal case that was never treated symptoms had apparently been present for almost 10 months. However, in another patient, who died as the result of irreversible cardiac failure and embolic nephritis, treatment with penicillin was carried out at home for only 1 month (presumably in ignorance of the correct diagnosis), and the patient gradually succumbed to the effects of *Hemophilus influenzae*; the organism in this case was belatedly controlled with streptomycin.

"Bacteriology.—No significant difference was noted in the bacteriology of the two groups. Alpha-hemolytic streptococcus was the predominant organism, but the gamma type occurred occasionally. Four patients with infections due to *Staphylococcus albus*, 1 with infection due to a beta-hemolytic streptococcus, 1 with infection due to *Streptococcus faecalis* and 2 with infection due to *H. influenzae* recovered. Eight patients with endocarditis caused by alpha-hemolytic and gamma-hemolytic, streptococcus and 1 with infection due to alpha-hemolytic, beta-hemolytic and gamma-hemolytic streptococcus also recovered. *Staph. aureus* was encountered only in the cases of acute endocarditis."

"Antibiotics.—All patients were treated with penicillin, and some received streptomycin in addition. Sulfadiazine was used in a few cases, and aureomycin in 2. The dosage of penicillin varied; in general, the largest amounts of the drug were given to the sickest patients, including those who died." With 1 exception (301,000,000 units given before death) the average total dose of penicillin in the well treated cases regarded as therapeutic failures during 1944-1946, was 35,000,000 units. "In the subsequent three year period the patients in whom therapy was considered a failure received an average dose of 80,000,000 units. Those who recovered, averaged 60,000,000 units. The largest total dose was 516,000,000 units combined with 38 Gm. of streptomycin. This resulted in a cure in a patient with a resistant *Staph. albus* infection. The largest daily dose was 30,000,000 units.

"Nutritional Status.—The nutritional state reflected the degree of illness and, as expected, was worst in the sickest patients. Of those who died 49 per cent were poorly nourished, and 20 per cent fairly well nourished, and only 31 per cent were well nourished. Among those who recovered, only 6 per cent were poorly nourished, and 31 per cent were fairly well and 63 per cent well nourished.

"Cardiac Status.—In all patients of this group subacute bacterial endocarditis was, as far as could be determined, superimposed on preexisting valvular or congenital heart disease, or both. The valvular changes were almost exclusively rheumatic. Two patients were considered to have clinical evidence of calcareous aortic stenosis. Syphilitic heart disease was not seen, although positive blood serologic findings were encountered in 2 cases.

"Congenital heart defects were present in 5 patients who died, an incidence of 22 per cent, and in 5 who lived, an incidence of 9 per cent. One lesion, congenital bicuspid aortic valve, was found in 4 cases at autopsy. It was suspected in a patient who also had a patent ductus arteriosus; this patient recovered. Tetralogy of Fallot was encountered in a patient who lived and in another who did not. Two patients with ventricular septal defects and 1 with pulmonary stenosis recovered. The surprising frequency of bacterial endocarditis on bicuspid aortic valves confirmed earlier observations that this defect is peculiarly vulnerable to infection. The combination, however, turned out to be more malignant than was anticipated. Curiously enough, despite the reported frequency of subacute endocarditis in coarctation of the aorta this lesion was not encountered at all in the 75 well treated cases, 16 undertreated or unrecognized cases and 6 patients with acute bacterial endocarditis.

"Except for congenital defects, the type and frequency of the valvular lesion were similar for the two groups. Changes in the mitral and aortic valves were found together in a third of all the cases. Pure mitral stenosis was the rarest abnormality and was seen only once in the entire series.

"Cardiac Arrhythmias: Auricular fibrillation was present with about equal frequency in the two groups. It occurred in chronic or transient form in 11 patients. Paroxysmal auricular tachycardia was noted briefly in a patient who subsequently recovered.

"Cardiac Enlargement: Evidence of cardiomegaly on x-ray examination proved to be a useful prognostic sign. The presence of significant enlargement was found in 71 per cent of the fatal cases and in 47 per cent of the patients who were cured.

"Cardiac Failure: A rather more impressive difference was seen in the relative incidence of myocardial insufficiency. Evidence of frank failure was apparent at some time during the course of the illness in 75 per cent of the unsuccessful cases. Minor decompensation occurred in another

9 per cent, and no failure was present in the remaining 16 per cent. By contrast, obvious failure occurred in only 13 per cent of the cured cases, and lesser degrees of decompensation in another 4 per cent. This single manifestation most nearly paralleled the final results, and its presence generally indicated an unfavorable prognosis.

"Renal Status.—Renal failure, the result of embolic nephritis, was seen in 3 fatal cases. It was the sole cause of death in 1 patient but occurred together with congestive heart failure in the other 2. Significant nitrogen retention was not encountered in the patients who recovered."

The causes of death in 23 adequately treated cases of subacute bacterial endocarditis were as follows: congestive heart failure, 10 cases; congestive heart failure and uremia, 2 cases; congestive heart failure and cerebrovascular accident, 1 case; cerebrovascular accident, 4 cases; uremia, 1 case; pulmonary embolism, 2 cases; ruptured splenic abscess, 1 case and cause unknown, 2 cases.

The Use of Digitalis in Spite of the Presence of Ventricular Tachycardia — GILSON, J. S. AND SCHEMM, F. R.— *Circulation*, 2: 278 (August) 1950.

"The presence of ventricular tachycardia has been regarded as one of the major contraindications to the use of digitalis." The writers' clinical observations, however, have led them to use digitalis somewhat more freely in cardiac disease in general than is usually recommended. The four observations on 3 patients presented illustrate instances of the intensive use of digitalis in the presence of ventricular tachycardia.

"It is not assumed that the digitalis in these instances stopped the tachycardia, but its use, along with other supportive measures, was followed by marked clinical improvement and the cessation of ventricular tachycardia. These results were not to be expected from the usual literature on digitalis or ventricular tachycardia." In the writers' observations, signs and symptoms which could be attributed to digitalis intoxication (nausea, vomiting, diarrhea and ventricular tachycardia) disappeared with the intensive use of digitalis, indicating that those signs, including the ventricular tachycardia, were not due to digitalis effect or to digitalis intoxication.

"Observation 1.—Case 1: L. G., age 53, a rancher. Admitted May 21, 1940. The tachycardia began 13 days after admission for symptoms and findings diagnostic of an acute myocardial infarction in an anterior position. The postinfarction period was characterized by one week of low grade fever, leukocytosis and by recurrent anginal pain up to the onset of the ventricular tachycardia.

"On the evening of the thirteenth day following admission (at 8 P.M. on June 3, 1940), after sitting up in bed for the first time that afternoon, the patient noted palpitation and discomfort in the chest with pain. There were no significant physical findings. The rectal temperature was 98.4 F. The heart rate was 128 per minute; the rhythm was regular.

"Before the electrocardiogram was read the patient was given 10 cat units of digitalis in 24 hours. When ventricular tachycardia was recognized as the mechanism, quinidine sulfate was administered. A total of 3.5 Gm. was used in 48 hours. The quinidine was discontinued when tinnitus, vomiting and a broadening of the QRS complex developed. Because the signs of heart failure were progressive and pulmonary edema developed, digitalis was resumed on the evening of June 7, four days after the onset of tachycardia. A total of 24 cat units was given by vein, with improvement in the signs of failure after 16 cat units and cessation of the tachycardia 4 hours after the twenty-fourth cat unit, 72 hours after the digitalis had been resumed. The tachycardia had lasted 176 hours, ending at 4 A.M. June 11. Nausea and vomiting ceased 24 hours after the ventricular tachycardia had stopped, in spite of the continuation of a maintenance dose of digitalis.

"Digitalization was maintained for the next six years until death resulted from another acute myocardial infarction. No subsequent episodes of ventricular tachycardia were observed. The autopsy demonstrated an extensive old, and a smaller recent, infarction."

"Observation 2.—Case 2: J. B., age 72, a retired cattle buyer. Admitted July 8, 1948. The episode of tachycardia began

on July 9, 1948 at about 9 P.M., 21 hours after admission to the hospital. Admission had followed a two day history of pressure-like chest pains lasting up to three hours and only partially relieved by rest, but totally relieved by morphine. During the first 21 hours of admission he was asymptomatic and showed a heart rate of 62 to 69 beats per minute with no irregularity. The blood pressure was 112/68. The lung fields were clear. While reaching for a glass the patient noted a sudden strange sensation, totally dissimilar to his previous anginal pain. He was conscious of rapid beating of his heart, felt giddy, faint, and nauseated. Apprehension was marked.

"Four years previously an acute myocardial infarction had been associated with a complete heart block and syncopal attacks, which were treated not only with adrenaline, but also with digitalis because of myocardial failure. The heart block disappeared and he was discharged on a 'maintenance' dose of digitalis. He had been admittedly somewhat lax in taking it in the intervening four years.

"At the beginning of the tachycardia the heart rate was 180 per minute and regular, although the radial pulse was so uneven in force as to simulate auricular fibrillation. . . . Heart tones were distant. The blood pressure was 102/70. The lung fields were clear.

"The electrocardiogram, taken one hour after the onset, showed a characteristic ventricular tachycardia although clearcut P waves could not be identified. With the previous case in mind, 0.4 mg. of digitoxin was given intravenously. Thirty minutes later a normal rate had reappeared and a normal mechanism was shown by the tracing together with changes compatible with a posterior myocardial infarction of indeterminate duration. Two hours after this electrocardiogram and 12 hours after the first episode another attack of tachycardia occurred, only to cease spontaneously in 30 minutes.

"The patient was then digitalized, receiving 1.0 mg. of digitoxin by vein in 18 hours, in addition to the 0.4 mg. given by vein with the first paroxysm of tachycardia. The nausea and vomiting associated with the attacks subsided during this completion of redigitalization. The following evening, on July 11, after another 0.2 mg. of digitoxin had been given by vein earlier in the day, another episode of tachycardia occurred. The patient was terrified; a reversion to normal rate occurred after morphine was given.

"Digitalis was continued without further incident. He was treated as a case of recent myocardial infarction and discharged on his twenty-ninth hospital day to continue his convalescent care at home. Digitalization has been maintained with from 1.0 mg. to 1.4 mg. of digitoxin per week, faithfully taken. During the past year and a half there has been no recurrence of palpitation or chest pain."

"Observation 3.—Case 3: A. T., age 54, crane operator. Admitted November 18, 1948. Extreme palpitation and malaise, sweating and apprehension, without pain, began about 18 hours before admission.

"Fourteen months earlier, in September 1947, a severe myocardial infarction had occurred after one month of anginal pain. A pericardial friction rub persisted for 10 days; arrhythmias, including auricular fibrillation and multiple ventricular premature beats, demonstrated by electrocardiogram, occurred intermittently; fever, without other demonstrable cause than the infarction and pericarditis, persisted for one month. Leukocytosis and the elevated sedimentation rate gradually subsided over a four week period. The ECG was compatible with a diagnosis of anterior myocardial infarction. He was digitalized in the first week and was maintained for the intervening year on 1 cat unit of digitalis leaf taken with religious regularity.

"This first episode of ventricular tachycardia began on November 16, 1948, one week after returning to very light work. On examination the temperature was found to be 101.2 F., the heart rate 160 and regular, the blood pressure 120/100. His face was ashen and covered with cold sweat. Respirations were rapid and grunting but the lung fields were clear. The heart sounds were faint and rapid. The white blood count was 23,000. The electrocardiogram showed a ventricular tachycardia.

"He was given the usual supportive measures for myocardial infarction, and dicumarol after the diagnosis of a fresh infarction was established. No quinidine was used." On the contrary, he was re-

digitalized because of the writers' experience in the preceding observations and their belief that patients frequently become insufficiently digitalized on the smaller daily doses of digitalis. "Digitoxin, 2.0 mg., was given by vein over a 30 hour period without any effect on the tachycardia. During the entire 30 hours, sweating, apprehension and agitation, and nausea with vomiting persisted despite phenobarbital and morphine. Rales became profuse over the lower lobes of both lungs. Because of the obvious increasing myocardial failure digitalis was continued. Two hours after the next dose of digitoxin which brought the total amount up to 2.2 mg. the mechanism reverted to normal with an apex rate of 90. Immediately his sweating, apprehension, and nausea ceased. In the next 10 hours the rales cleared rapidly; they disappeared in 36 hours.

"With the reversion to normal rhythm a fresh infarction was suggested by the electrocardiogram. He was maintained on digitoxin, 0.2 mg. daily, and discharged on the twenty-third hospital day, the hospital program being continued at home."

"Observation 4.—Case 3: A. T. (same patient as above). Admitted April 29, 1949.

"He had been on markedly restricted activity for six months since recovery from the first attack of ventricular tachycardia and his second myocardial infarction described above. He had been faithfully taking digitoxin, 0.2 mg. daily, since the previous attack.

"This second episode of ventricular tachycardia began with palpitation and 'uneasiness' about 11 P.M. April 28, 1949 following a quiet visit with two friends. There was no pain.

"On examination (April 29) the rectal temperature was 100 F. The heart rate at the apex was 170 and regular, but the radial pulse exhibited irregular force as noted in Observation 2. The heart sounds were of fair quality. No rales were heard at the bases of the lungs. The white blood count was 15,500. The electrocardiogram showed a ventricular tachycardia.

"Because the effect of quinidine, in what was thought to be a third infarction, was feared even more than the effect of digitalis and because the previous attack of ventricular tachycardia had responded coincident to rapidly given digitoxin in a total dose of 2.2 mg., digitoxin was again given intravenously when morphine and sodium phenobarbital had given no relief. During the first 53 hours 2.6 mg. of digitoxin were given intravenously with no effect on the tachycardia. He vomited three times after the first dose of digitoxin but had no nausea or vomiting thereafter. During this 53 hour period he became febrile, complained of substernal heaviness, and finally developed pulmonary edema, which subsided in 3 hours coincident to the use of tourniquets, phlebotomy, and a positive pressure mask. The pulmonary edema recurred 16 hours later." At this recurrence quinidine lactate was begun but was halted after 0.4 Gm. had been given because of rapidly increasing irregularity in pulse, cyanosis, and coma. "He gradually improved in the succeeding 12 hours.

"Although digitoxin was continued, quinidine lactate was again given intravenously on May 2 and 3 (the fourth and fifth days of the tachycardia). Doses of 1.3 Gm., followed in 8 hours by 2.0 Gm., and in 24 hours by 2.0 Gm. were given intravenously in 5 per cent dextrose solution at a rate of about 0.5 Gm. of quinidine lactate per hour. The heart rate slowed progressively with each administration of quinidine, and an apparent broadening of the QRS complexes and reversal of the major deflections of QRS in leads I and II occurred. In one record taken during these transient (one to two hours) slowings, P waves are clearly seen at a rate of 68 with a ventricular rate of 150 per minute. He became distinctly and progressively irrational during each administration of quinidine; and was controlled only for one to two hours by phenobarbital or morphine. Basal pulmonary rales persisted; cyanosis increased. One Gm. of potassium chloride was given intravenously on the evening of May 3 with no apparent effect.

"He had received 3.7 mg. of digitoxin, 5.7 Gm. of quinidine, and 1.0 Gm. of potassium chloride when, on May 4, at 8 A.M., 112 hours after admission and 128 hours after symptoms had begun, his rate suddenly dropped from 200 per minute with a regular rhythm, to 92 with an irregular rhythm. . . . This occurred 20 hours after the last dose of quinidine and 24 hours after the last dose of digitalis.

"The next day, five and one-half days after admission, his rhythm was regular and the electrocardiogram showed a sinus rhythm with a rate of 90 per minute. The tracing of May 7, 1949 showed changes indicating a fresh infarction.

"Within 60 hours after reversion to normal rhythm his general improvement was marked. Digitoxin, 0.2 mg., and quinidine, 0.6 Gm. daily, were continued as he convalesced uneventfully. In the nine months since his discharge on the thirtieth hospital day, there has been no recurrence of heart failure or tachycardia with 0.6 Gm. of quinidine daily and a heavy maintenance dose of 1.8 mg. of digitoxin per week."

"The survival of these patients for prolonged periods suggests that support of the failing myocardium with digitalis may be an important aspect of treatment in prolonged ventricular tachycardia."

A Simple and Suitable Staining Method for Cytologic Cancer Diagnosis from the Vaginal and Cervical Secretion— CRAMER, HERBERT AND STAMM, DANKWART — *Geburtshilfe und Frauenheilkunde*, 10: 676 (September) 1950.

Any method of cytologic examination of the vaginal secretion for cancer cells and groups of such cells if to be applied to a large number of patients must be simple and rapid, and must at the same time furnish clear cellular pictures which lend themselves to reliable interpretation. The nuclear structures (size, shape, and chromatin contents and distribution) and also the nucleus-protoplasm ratio of the cells are of the greatest importance in this respect.

In the authors' clinic apart from Papanicolaou's original method the hematoxylin-eosin and the Pappenheim staining methods were used, the latter in the original form and in a modification. From a comparison of the advantages and disadvantages of these methods the authors draw conclusions concerning their own technic.

Papanicolaou's method furnishes excellent cellular pictures with fine nuclear structures, the epithelium is readily recognized even on relatively low magnification, and atypical epithelial cells and groups of such cells are usually recognizable even on medium magnification, but reliable pictures are obtained only when the staining is carried out with the greatest care; thus the sensitivity of the method has a certain disadvantage with respect to large scale application as one or even several workers are required in a highly concentrated manner.

With the simpler hematoxylin-eosin staining method the most important sign of malignancy in small atypical epithelial groups from vaginal smears; namely, the nuclear variability, is well demonstrated, but the finer cellular and nuclear structures are not visualized as clearly as with Papanicolaou's original method; there is the additional disadvantage that the color of the cytoplasm of the normal and carcinomatous epithelial cells differs little from that of the other components of the secretion, and the search for suspected or definite cancer cells is more difficult due to the accidental distribution of the epithelial cells in smears as opposed to that of tissue sections.

Cytodiagnosis of cancer in peritoneal and pleural exudates, sputum and gastric juice has been tried with various methods before, including the Giemsa and May-Grünwald stains, vital staining methods, and a phase contrast method, the latter requiring immediate examination of the fresh material and not affording preservation of the material for subsequent comparisons unless photographs are taken.

The authors tried the Pappenheim method which is most widely used for blood pictures and which visualizes the finer nuclear and plasmatic structures of the blood cells very well; the method has the advantage of great simplicity. However, on using the Pappenheim method for vaginal and cervical secretions a disadvantage is encountered in that cell groups take up too much methylene blue, so that with the concomitant relatively intense staining of the cytoplasm evaluation of the nuclear shapes and structures at the margin of the cellular complexes becomes very difficult or even impossible. If the secretion includes mucus, as usually the case in cervical secretions, the mucus will also stain with the methylene blue and will cover the cellular pictures. This disadvantage could not be eliminated by changes in the length of staining and in the concentration of the methylene blue.

A study of the theory of staining shows that the cellular organs and structures which are demonstrated by staining methods are chemically proteins. In their physicochemical behavior these proteins are ampholytes; that is, they have alkaline properties in an acid and acid ones in an alkaline medium. The *p*H at which they dissociate as many H as OH ions and therefore have neutral properties is termed the iso-electric point, and the latter differs for different proteins. It has been observed that the same cellular portion stains with acid stains in the acid and with basic ones in the basic range, with a change of color at the iso-electric point; thus the notions of acidophilia and basophilia are deprived of their absolute validity, and they apply only to a certain range of the *p*H of the staining fluid. Therefore it was to be expected that the intense staining of the cellular groups and the mucus with methylene blue could be prevented by letting this basic dye act in an acid medium. The Giemsa solution is in the acid range, with a *p*H of 6.24, while the May-Grünwald solution lies in the alkaline range, with a *p*H of 8.91 in the dilution corresponding to the Pappenheim method. Furthermore, the *p*H of the two solutions is not constant and changes with dilution.

By addition of buffer solutions of high capacity to the water for dilution of the dye solutions and the water used for rinsing the milieu during the process of staining could be adjusted to a certain *p*H. Sorensen's phosphate buffer was used, and with a *p*H of 6.1 the best pictures were obtained from tumor cell groups with several layers, disregarding particularly thick tumor fragments.

For making a large series of preparations the authors advise the following procedure: The glass slides are cleaned and freed of fat, and then covered at one end with citrate blood with a brush; after drying the data can be written on this blood with a soft pencil and will be preserved throughout the staining process. Fixation is best done in a mixture of equal parts of ethyl alcohol and ether, or in ethyl or methyl alcohol alone. The still-moist smears are placed into the bowls with the fixation fluid and may be kept there until staining. The minimal fixation period is 20 minutes.

Utensils for the staining method include a round glass bowl of 20 cm. diameter and 2 cm. height with enough space for 13 glass slides, a pipette of 5 cc. for the Giemsa solution, two cylinders for preparation of the May-Grünwald and the Giemsa solution, a washing bottle for the buffer solution and forceps.

Solutions required include the May-Grünwald solution (eosin-methylene blue), the Giemsa solution (azure eosin-methylene blue) and the phosphate buffer solution. For preparation of the latter 45.39 Gm. of KH_2PO_4 are placed into one measuring glass of 1,000 cc. capacity and 59.38 Gm. of Na_2HPO_4 into another one; distilled water is added up to 1 fingerbreadth below the mark and the solutions are left to stand for several days before use and then filled to the mark. One-third molar solutions are dealt with. For actual use the buffer solutions are mixed in a ratio which corresponds to the *p*H desired, and then the mixture is diluted with seven volumes of distilled water; this final solution is used for dilution of the dyes and for rinsing. The ratios for various *p*H are tabulated; they range from 2.5 cc. of the sodium and 97.5 cc. of the potassium salt solution for a *p*H of 5.3 through 15 cc. of the former and 85 of the latter for a *p*H of 6.1 to 70 cc. of the former and 30 of the latter for a *p*H of 7.2. The third molar solutions keep for a considerable length of time.

The staining is done as follows: The preparations are placed into a dry glass bowl. The original May-Grünwald solution is diluted with an equal amount of the buffer solution adjusted to a *p*H of 6.1 and poured over the preparations. Staining is continued for two minutes with slight agitation. The dye is poured off and the preparations are rinsed clear with the buffer solution. A freshly prepared Giemsa solution (4 cc. of the original solution diluted to 100 cc. with the buffer solution) is poured over the preparations and staining is continued for 15 minutes. The dye is poured off and the preparations are rinsed clear with buffer solution. The preparations are left to dry in air; then they are dipped for a short period in xylol and covered with "Caedax."

It is possible to stain in two bowls at the same time without difficulty. During the Giemsa stain of the first series of 13

preparations the May-Grünwald stain of the second series may be started.

The epithelium will show a red to blue cytoplasm and blue to purple nuclei, leukocytes and erythrocytes will appear as in a blood picture, and bacteria will appear blue. This staining method differs from Pappenheim's method by the greater concentration of the Giemsa solution and the use of the buffer solution for dilution and rinsing. With these modifications the theoretic expectations could be fulfilled and the disadvantages of the Pappenheim method for the purpose under consideration could be largely eliminated. In cancer cell groups the protoplasm stains only slightly blue and shows some thready structures; thereby the nuclei are well visualized and are not covered up by intensely stained protoplasm. Mucus stains hardly at all, and usually pale pink, so that cellular elements located in the mucus are well visualized and can be readily interpreted. The epithelium stands out well from the other components of the secretions. In addition the bacteria stain and the degree of purity can be evaluated, even in cervical secretions with a great deal of mucus. The authors believe that this method is simple and suitable for cytologic diagnosis of uterine cancer in large scale examinations.

Lysivane Therapy for Parkinsonism — PALMER, HAROLD AND GALLAGHER, D. J. A. — *British Medical Journal,* 2: 558 (September 2) 1950.

This paper reports the writers' experience with 16 patients with parkinsonism treated with lysivane.

"The drug is supplied in 0.05 Gm. tablets. All patients, in the course of one week, were placed on their characteristic effective dose, which varied from 4 to 10 tablets a day." At first the writers confined their maximum to 5 tablets daily, but it seems that this leaves a very large margin of safety and some patients did not achieve maximum benefit on this dosage. Up to 20 tablets a day have been used by one writer. In view of the fatality encountered with the use of diparcol the writers have been cautious. They believe that, as further experience is gained and more is known about the clinical toxicity of these drugs, a higher dose may be permissible and better results than those they are recording will be achieved.

"Rigidity responds better than tremor when the two occur in combination. Tremor alone responds best of all."

The writers believe that restoration of that controlled background of muscular tone upon which all voluntary movement is based determines the favourable response to lysivane, though some degree of tremor may persist. "Festination and retropulsion disappear, the patient ceases to be the important claimant on his relatives' attention, and the tremor becomes a matter of the transient emotional tension to which even normal individuals are prone."

The most striking case, and one which illustrates the importance of viewing a patient as a whole as opposed to estimating the effect of the treatment on symptoms, is the following: "On admission to hospital this patient resembled a senile dement. She was confined to bed in a rigid, hopeless state, with little contact with the outside world, and with all the implications which this state of affairs had for the nursing staff of the home for the aged where she was being nursed. She walked out of hospital unaided, had assumed quite a charming personality, and returned to the home to gladden the hearts of her fellow patients and to encourage the staff in their humanitarian care of the aging and chronic sick." In a case like this, one does not feel disposed too narrowly to estimate benefit in terms of isolated symptoms alone.

Of the 16 cases, 12 were treated as outpatients, receiving no other form of therapy. The remainder while in hospital may have derived benefit from rest in bed and the physiotherapy which was given. "One patient suffering from postencephalitic parkinsonism and showing tremor, oculogyric crises, and festination, who had received surgical treatment in the United States of America which relieved all symptoms, except bradyphasia and depression (partly due to a postoperative complication of focal epilepsy), obtained no benefit from lysivane.

"Toxicity.—The laboratory findings of the French workers place the available drugs in the following descending order of toxicity (in rats): phenergan, diparcol, lysivane."

As the writers have had no deaths with lysivane in spite of 1 patient stopping the treatment suddenly, and in view of the 1 fatality with diparcol, the writers infer that their experience bears out the laboratory findings.

"Clinical toxic events are as follows: (1) Drowsiness and lassitude, with or without vertigo, appearing half an hour after dosage and lasting one or two hours, most apparent early in treatment. These effects eventually disappear and are countered effectively by strong coffee or by amphetamine sulphate. (2) Formication, irritation, and cramps are paraesthesias related to parkinsonism rather than to drug therapy. These are perhaps, strictly speaking, not toxic effects so much as release phenomena consequent upon the treatment of the basic condition. They are relieved by aspirin and disappear in some weeks. (3) Dryness of the mouth, transient diplopia, vasomotor reactions; these are rarely found, and disappear spontaneously.

"In the present study only the first group of toxic symptoms was observed and in no case was it necessary to discontinue treatment." In one writer's series 6 out of 106 patients treated suffered vertigo or cramps, necessitating discontinuation of treatment.

"An interesting feature was the tendency for patients to show a marked initial improvement followed by some relapse and then a final upward movement until stability had been reached. This probably refers to the placebo effect of encouragement which operates at a maximum initially.

"One case previously treated with diparcol gave an improved response to lysivane."

One writer has recorded, however, that lysivane was greatly superior to all other forms of treatment in 46 out of 106 cases, identical in 29, and inferior in 4.

"One of the advantages of lysivane therapy is that the drug can be combined with other forms of treatment—for example, stramonium." Indeed, in 2 cases which had previously derived benefit from stramonium, lysivane alone was to some extent disappointing, though improvement undoubtedly occurred. "When, however, the two drugs were given in combination the final effect was far superior to that achieved by stramonium, or, indeed, by either one separately. It would seem, therefore, that patients suffering from parkinsonism should also be tried with lysivane in combination with stramonium.

"With lysivane alone 1 patient who suffered from oculogyric crises, and who formerly had had attacks daily, had the attacks reduced to one or two a week.

"All the remarks concerning withdrawal which apply to diparcol apply by inference to lysivane, but one old lady stopped her treatment while having 5 tablets a day, with no untoward result. For the time being, however, it would seem to be mandatory that all patients should be carefully instructed never to withdraw the drug suddenly."

"Lysivane is capable of affecting beneficially any symptom or complex of symptoms from which the parkinsonian patient is suffering—notably his mentality." The writers would estimate their findings in general as follows: complete alleviation, 1; good result, 10; improved, 4; and no change, 1 (patient and relatives concurred in cessation of further treatment).

The writers wish, however, once more to reiterate the dangers of attempting to evaluate results on too narrow a symptomatic basis and are content to assert that in their opinion lysivane does all that is claimed for it in a manner which is safe for the patient. "It may confidently be recommended, therefore, as a valuable remedy in the treatment of this condition."

A Prolonged Study of Oral Veratrum Viride in the Treatment of Essential Hypertension—McNair, J. Douglas, Griffith, George C. and Elek, Stephen R. — *American Heart Journal*, 40: 382 (September) 1950.

"A group of 22 patients with essential hypertension was treated with *Veratrum viride* in tablet form for periods varying from two to five months. Each patient was given the maximum dose he could tolerate and was used as his own control by substituting placebos for the drug."

"The patients were usually started on 20 units daily, one tablet in the morning on arising and the other at the evening meal. The observations were made at the clinic approximately three to six hours after the morning dose. The dose was rapidly in-

creased to the patient's tolerance, which was the maximum amount the patient could take without having more than slight nausea. The daily maximum dose varied from 60 to 120 units, or 6 to 12 tablets, and averaged 82 units per patient for the group. The maintenance dose was about 20 units less as symptoms were produced with the maximum amount."

On comparing the average blood pressure untreated and with placebo tablets with the average blood pressure with Veratrum, 16 of the 22 patients showed a drop in both systolic and diastolic pressure. "Three patients showed a drop in diastolic pressure and a fall in systolic pressure, and 2 patients showed a rise in both systolic and diastolic pressures. The average over-all change (comparing the averages of all patients) showed a fall of 7 mm. Hg in the systolic and 6.6 mm. Hg in the diastolic blood pressure. Considering both systolic and diastolic pressures together, the poorest result was in a patient whose systolic pressure rose 9 mm. Hg and whose diastolic pressure fell 25 mm. Hg and 14 mm. Hg, respectively.

"On comparing the average pulse rate before and during treatment, the over-all change showed a drop of 3 beats. Sixteen patients' pulse rates fell with treatment; 5 patients' pulse rates rose. The range was a fall of 13 to a rise of 14 beats.

"Symptomatically, 6 patients claimed they felt much improved; 5 felt slightly improved; 10 felt unchanged; and 1 felt worse with treatment."

Looking at these results from a slightly different point of view, from a survey of the observations of blood pressure in different categories rather than from a comparison of patients, one can test the significance of the results. The only appreciable fall, as demonstrated by a comparison of these means, was in the systolic sitting pressure, before and during treatment, of 15 points. The blood pressure records taken in the lying position did not seem to show a tendency to be lower than in the sitting position.

"Is the fall of 15 points in systolic pressure significant?" The writers would not think so because: (*a*) under Veratrum, the systolic blood pressure was 5 points higher when the patient is lying than when he is sitting; and a comparison of systolic blood pressures with the patient lying, before and after treatment, showed a drop of only 5 points; (*b*) there was a great variation in the systolic blood pressure before treatment; almost every patient showed a change, both up and down, of 30 to 40 points, and 1 even showed a change of 80 points; (*c*) the standard deviation of the group of untreated systolic blood pressure records, with the patient sitting, was 31.6, which is extraordinarily high, indicating a great variability. "A fall of 15 points would not even indicate the usual amount of change that one might expect in this group."

"Is a fall of 9 points in the diastolic pressure significant?" Again the writers would not think so because: (*a*) again there is a great variation, even in this more stable pressure, before treatment; a shift of 20 points is not unusual; (*b*) the standard deviation of the group of untreated diastolic blood pressure records, with the patient sitting, was 13.54, which is still quite a high figure, indicating a considerable inherent variation in the observations; thus a fall of 9 points would be entirely a change which one could expect, even before treatment.

"The same line of reasoning can be applied to the other groups, since the blood pressures taken in the lying position seem to vary just as much as those in the sitting position." The number of observations under placebo treatment were too few to be significant, but the mean readings of these groups were within 10 points of both the untreated and treated groups, and thus do not show any clear trend.

"Objection may be raised to the manner of obtaining the average blood pressure during treatment. It might be said that since the blood pressure is lowered only at a critical level of dosage, all other readings taken with smaller dosage should be excluded or should be included with the control readings. This possibility was not considered originally, and they were grouped in this way in order to have as many readings as possible in each group so that when averaged together unusual fluctuations would not too greatly affect the results obtained. . . . Quite often the blood pressure was higher with the maximum dose than the following week when the patient was on placebo."

"The possibility of poor absorption of the tablets was also considered, but when the same drug was given to hospitalized patients for a short time a definite hypotensive effect was obtained in some of them. This latter group of patients has not yet been studied thoroughly enough to reach any definite conclusions; however, there is indication that the drug is fairly well absorbed and also that for at least a short time a hypotensive effect may be obtained." Therefore, although the writers cannot explain their results in this study, a possible explanation may be the phenomenon of tachyphylaxis.

The writers' conclusion, therefore, is that *Veratrum viride* in the form used did not show any significant hypotensive effect in essential hypertension over a prolonged period, but should be further investigated, particularly in acute conditions.

The "Milk Factor" in Carcinoma of the Human Breast. An Analysis of 88 Cases — Horne, Herbert W., Jr. — *New England Journal of Medicine*, 243: 373 (September 7) 1950.

"Case histories of well over 1,000 women with known carcinoma of the breast were made available by several hospitals. The report of the pathologist who examined the tissue was accepted as confirmation of the diagnosis. From these cases were chosen 88 patients who, together with their mothers, were still living. As a control group, a similar selection was made of 86 patients who had had vaginal plastic operations performed at this hospital, and in whom no neoplastic process had been discovered from the history, physical examination or pathological examination. The average age of the two groups was the same. Explanation of this unanticipated feature seems to be that though both conditions under study usually occur in the later decades of life, only patients whose mothers were still living were included in the report.

"To all these patients letters were sent explaining, so far as possible, the purpose of the study and asking that they have their mothers personally fill out an enclosed questionnaire. The information requested covered the mother's name and address, general health, age and history of tumors in herself. The specific question was then asked whether or not she nursed the patient. She was definitely informed both in the letter and on the questionnaire that a single, though perhaps unsuccessful attempt to nurse the daughter required an affirmative answer. She was also advised that if there were any doubt in her mind, she should not answer the question at all. Under these circumstances, a personal interview was arranged. Request was made for a maternal family history regarding the incidence of tumors and known cancer among the patient's great grandmother, grandmother, aunts and uncles, as well as her siblings, with ages or ages at death.

"Since it has been shown experimentally in mice that a minimal quantity of infected milk can transmit the neoplastic tendency to the female offspring, it was necessary to establish two strict rules for answering the questionnaires. The first was that the patient's mother must give the information in every case. The second was that if the mother stated that she had not nursed the patient, a reason for this must be obtained either by personal interview or by detailed letter. Thus, confirmation that she had not nursed the patient even once was received. Also, other possible sources of human breast milk, such as wetnursing and breast milk banks, were eliminated. In a few cases an originally negative reply became affirmative under this close scrutiny. A few other cases of probable negative replies were eliminated from the study for lack of a recalled definite reason why nursing had not been attempted. . . . In all the cases reported the mother was sure that the daughter in question had never been allowed any human breast milk."

"The incidence of absence of breast feeding in the 88 cases of known cancer of the female breast is compared with that in the 86 cases of vaginal plastic surgery. Among the patients with cancer, 9 had never received any human milk. Among the patients who had had vaginal plastic operations 7 had never received any human breast milk. The average age of the patients with cancer was 41.375 years, with a range of 23 to 66 years, and that of the patients with vaginal plastic operations 41.395 years, with a range of 26 to 61 years.

"Among the maternal family histories of the patients with cancer, exclusive of the patients' neoplasms, a total of 87 tumors, of which 20 were known cancers, were reported. Four of these cancers were in mothers of patients under study; 1 was of the breast, 2 of the intestines, and 1 of the skin. Among the maternal family histories of the patients who had had vaginal plastic operations a total of 35 tumors, of which 14 were known cancers, were reported. Only 1 of these cancers was in the mother of a patient under study: a cancer of the skin."

The Streptomycin Treatment of Endocarditis Lenta — WOLLHEIM, E. AND KLEINFELDER, H. — *Deutsche medizinische Wochenschrift*, 75: 1121 (September 1) 1950.

While the Anglo-American authors reported extremely favorable results with the penicillin treatment of endocarditis lenta in high dosage (67 per cent according to one author), German authors reported much lower percentages of cures (20 per cent according to one author). It seemed therefore rational to test the effect of other antibiotics in endocarditis lenta.

A year ago the authors started to use streptomycin in cases of endocarditis lenta which did not show a definite healing tendency with the usual dosage of 800,000 to 6,400,000 units of penicillin. The streptomycin was given in a daily dosage of 1 Gm. up to a total of 30 to 90 Gm. and with this dosage side effects on the part of the vestibular nerves have not been observed. In case of cutaneous signs of hypersensitivity the streptomycin may be replaced by dihydrostreptomycin, and an antihistaminic may be given at the same time.

A total of 10 patients with endocarditis lenta have been treated in this manner; 1 patient succumbed right in the beginning of the treatment, and of the remaining 9, 3 were completely cured. The first of these cured cases involved a man, aged 28, with a history of scarlet fever with nephritis during childhood. The patient was in Russian captivity, under poor nutritional conditions, and was discharged from there in poor general condition with edemas, and allegedly with a valvular cardiac defect. Two years after discharge from captivity he developed weakness and fatigue; several weeks later subfebrile temperatures supervened, and a few months later he was admitted to hospital after a paralysis of his right side. Examination revealed regressing cerebral embolism with hemiparesis and hemianesthesia, mitral insufficiency, focal nephritis, and a firm spleen, extending 3 fingerbreadths below the costal margin. Together with anemia, a high sedimentation rate and a leukocyte count of 6,900 the syndrome was typical of endocarditis lenta. The blood culture revealed *Staphylococcus pyogenes aureus* which proved penicillin-sensitive in the test tube. Penicillin treatment was started with a daily dosage of 800,000 units and after nine days the dosage was increased to 1.6 million units, but the fever remained unchanged. After a total dosage of 17 million units, penicillin treatment was discontinued. Then four periods of 10 to 14 days each of "supronal" treatment were instituted, with a total dosage of 148, 124, 100 and 124 Gm. respectively, and in addition nine blood transfusions were given, with 100 to 250 cc. of blood. Defervescence was achieved but the sedimentation rate remained high, and spleen and focal nephritis were not influenced. The anemia was improved by the transfusions. A coronary embolism supervened, electrocardiographically demonstrated to result in an infarction of the posterior wall. The associated pericarditis developed into an exudative type, and at the same time massive hematuria supervened, probably due to multiple renal emboli. The general condition was alarming and streptomycin treatment was then instituted; the first treatment series lasted 30 days and on the sixteenth day the patient was afebrile. Later another series of 25 days duration was given, and at the end of the second series the pericarditis was healed. The sedimentation rate became normal, and the focal nephritis and the splenomegaly disappeared. The general condition improved and the patient gained weight. In spite of the myocardial infarction the picture was that of compensated mitral insufficiency, and the cerebral embolism had left no residue. There was no relapse during an observation period of seven months after clinical cure.

The second case concerned a clergyman, aged 34, who suffered from dyspnea on

effort after an attack of rheumatic fever four years earlier; fatigue, increased thirst, and nightly chilling supervened and small tender nodules appeared at the level of the finger tips leading to admission. The temperature was remittent between 37° and 39° C. Examination revealed mitral and aortic insufficiency, a hard enlarged spleen, a very high sedimentation rate, anemia, abundant erythrocytes in the urine, a nonprotein nitrogen level of 60 and a uric acid level of 8 mg. per cent, a positive indican reaction in the serum, hyposthenuria with a range between 1004 and 1010 on dilution and concentration test, and repeatedly negative blood cultures. The urine contained rods which could not be further differentiated and which were agglutinated by the patient's serum. Thus endocarditis lenta was dealt with, complicated by such extensive focal nephritis that the picture of renal insufficiency was produced. Penicillin treatment was started with 800,000 units daily and after seven days the dosage was increased to 1.2 million units; after a total dose of 12 million units penicillin treatment was discontinued as it was entirely ineffective. On the last day of penicillin treatment a severe apoplectic attack took place, with hemiplegia on the right side and loss of consciousness. The nonprotein nitrogen level rose to 110 mg. per cent. Streptomycin treatment was then started and the temperature decreased gradually leading to defervescence on the sixteenth day. For a short period of time during the third week of treatment the temperature rose again. Streptomycin was continued for a total of 65 days; the splenomegaly regressed, the hematuria subsided gradually, and the nonprotein nitrogen level fell to 37.8 mg. per cent. The sedimentation rate was still high at the end of the streptomycin treatment but subsequently fell gradually. After four weeks streptomycin was resumed for another 25 days and the sedimentation rate showed a further fall. The renal function improved and a specific weight of 1.025 was reached with the concentration test. Within another eight weeks the sedimentation rate became normal. The hemiparesis and the signs of motor aphasia improved but did not disappear completely. The splenomegaly regressed completely. Over an observation period of eight months no relapse of the infection occurred.

The third case concerned a man, aged 47, with a valvular defect after an attack of rheumatic fever at the age of 5. At the age of 23 the patient had syphilis and was treated with three series of injections of neoarsphenamine and bismogenol. Fatigue and fever supervened and another series of these injections was given without success in another hospital; there three series of penicillin injections were also given, with a daily dose of 160,000 to 320,000 units and a total dose of 11 million units, leading to gradual defervescence. Eight to 10 days after discontinuation of the penicillin treatment the temperature rose again. On admission examination revealed aortic and mitral insufficiency, slight splenomegaly, focal nephritis, a high sedimentation rate and anemia. In the blood *Streptococcus viridans* was demonstrable, and was shown to be sensitive to penicillin and streptomycin in vitro. The serologic syphilis reactions were partially positive. Treatment was started with potassium iodide, 0.1 Gm. three times daily for one week, in order to avoid a Herxheimer reaction, and then penicillin was given in a daily dosage of 800,000 units, up to a total of 30 million units. Defervescence and considerable improvement of the general condition were achieved, the focal nephritis subsided, the splenomegaly remained unchanged, and the sedimentation rate was only slightly reduced. The venous blood culture was negative, but from the arterial blood *Str. viridans* was again cultured five weeks after termination of the penicillin treatment. Streptomycin treatment was then started, first 30 Gm. and later another 20 Gm. Arterial and venous blood culture became negative, and the sedimentation rate fell considerably. Slight physical effort produced attacks of auricular fibrillation with paroxysmally high ventricular frequency, changing into a normal sinus rhythm with digitalis treatment (2 cc. of digitan intravenously). Otherwise cardiovascular compensation was established. Over an observation period of eight months no relapse occurred.

The remaining 6 patients were treated in a similar manner but without any clinical improvement; all of them showed abacterial forms of endocarditis lenta, 1 with

high fever, the others with little or no fever. While penicillin produced at least transitory improvement in all these cases, streptomycin treatment was completely ineffective. Thus in the first 2 cases penicillin treatment was ineffective, and in the first case the sulfonamide treatment influenced only the fever; embolic phenomena continued in both cases and the picture changed only after streptomycin treatment was instituted. In both cases all signs of infection disappeared completely but the valvular defects and the embolic phenomena left residue. In all 3 cases the onset of the endocarditis lenta did not date back more than five to six months, and in the first and third the causative agent could be demonstrated in the blood, while all cases resistant to streptomycin were abacterial and had a much longer history of the infectious stage. This suggests but does not yet prove that streptomycin, too, is more likely to be curative in cases with manifest bacterial genesis and in early cases with high temperatures. In any case the authors' observations show that in some of the cases in which penicillin does not control the infection within a relatively short period of time streptomycin treatment has a chance to control it. Chemotherapy should be started early in endocarditis lenta before valvular damage and embolic processes have occurred, and high doses of penicillin should be used; if after at least 30, and possibly 60 to 180 million units, with daily doses of at least 1.6 million units, no definite effect is observed on temperature, splenomegaly, focal nephritis, anemia, and particularly the sedimentation rate, penicillin should be discontinued and streptomycin treatment should be instituted without delay. In cases with high fever the change should be made even earlier if high daily doses of penicillin are ineffective. In every case with a valvular affection any signs of protracted infection should cause a suspicion of endocarditis lenta, and appropriate diagnostic and therapeutic measures should be instituted.

The authors also observed a good therapeutic effect of streptomycin in some cases of septic endocarditis while penicillin was ineffective; cases with a negative blood culture were dealt with while the clinical course indicated a septic process. The authors report 1 illustrative case of this type involving a man, aged 37, with a history of frequent tonsillitis. Four days before admission to hospital he developed high fever and pain in several joints. Examination showed reddening of the pharynx and tenderness of the joints, without reddening and swelling. The sedimentation rate was very high; the leukocytes numbered 25,000, with a 20 per cent shift to the left. Salicylates and aminopyrine failed to influence the fever. On the fourth day of treatment a systolic murmur appeared over the mitral area and increased in intensity subsequently. Repeated blood cultures were negative. Penicillin was started with a daily dosage of 500,000 units and later the dosage was increased to 1.6 million units. The progressively more severe syndrome was not influenced by a total of 14 million units, and splenic infarction, bilateral bronchopneumonic foci, and dry pericarditis developed during penicillin treatment. The severe syndrome of pancarditis with splenic infarction and high fever without demonstrable germs developed and streptomycin treatment was then started; from the second day of this treatment the temperature began to decrease and the leukocytes diminished in number. After a week, defervescence was obtained and the bronchopneumonic foci regressed. After three weeks, the sedimentation rate became normal, the pericarditis was cured, and a mitral insufficiency persisted as residue of the endocarditis, with slight decompensation which improved under digitalis treatment. Particularly when in septic endocarditis the causative germ cannot be demonstrated and when penicillin proves ineffective, streptomycin seems indicated.

It cannot as yet be decided whether a distinction will have to be made in the future between the older classic conception of endocarditis lenta and subacute septic forms of endocarditis with a similar course.

Sickle Cell Anemia in the White Race— Guyton, Richard A. and Heinle, Robert W. — *American Journal of the Medical Sciences*, 220: 272 (September) 1950.

"Sickle cell anemia is predominantly a disease of the Negro race, but both sicklemia and sickle cell anemia have occurred in persons in whom there can be no reasonable suspicion that admixture of Negro

blood has occurred. Fourteen well documented cases of sickle cell anemia occurring in white individuals have been recorded. Several other cases have been reported in which family studies were not done and in whom the possibility of the presence of Negro blood is strong. There is no doubt that both sicklemia and sickle cell anemia are inherited, but none of the prevalent genetic theories is applicable to all the reported cases. Further accumulation of data is desirable to establish the genetic pattern of the disease. This report describes the occurrence of sickle cell anemia in a white individual in whom all available relatives were studied for the sickling trait and sickle cell anemia."

Case Report.—L. N., a 19 year old Sicilian girl, was first admitted to hospital in April, 1949, complaining of fever, severe leg pain, dark urine and yellow eyes. "She had been treated with liver and iron since the age of 5 years for 'splenic anemia.' Her first known hemolytic crisis occurred 2 years previous to this admission with back and shoulder pain and dyspnea. She was found to have anemia, splenomegaly, and an elevated icterus index. The diagnosis of sickle cell anemia was first made in 1948, one year before this admission. A splenectomy was performed at another hospital following her fifth hemolytic crisis. The rationale for the splenectomy is not apparent. The patient was a poorly developed, jaundiced, young white female with no negroid characteristics. There were no leg scars and no adenopathy. Laboratory findings were as follows: Erythrocytes 2.97 million per cmm., hemoglobin 9.8 Gm. per 100 ml., hematocrit 31 per cent, leukocytes 21,000 per cmm., reticulocyte count 23 per cent, mean corpuscular hemoglobin 32 mcmcgm., mean corpuscular volume 103 cu. microns, mean corpuscular hemoglobin concentration 32 per cent. The platelets were slightly increased in number, as estimated from cover slip films. There was 100 per cent sickling of the erythrocytes in 24 hours in a paraffin-sealed wet preparation. Urine urobilinogen was 5 Ehrlich units in a 2 hour specimen. Total serum bilirubin was 4.42 mg. per 100 ml. of which 2.64 mg. was direct and 1.78 mg. indirect. Erythrocyte fragility began at 0.46 per cent saline and was complete at 0.28 per cent. Roentgenograms of the gallbladder revealed 4 laminated calculi, and of the tibia and fibula revealed a moderate degree of osteoporosis with loss of the normal trabeculation of the medullary canal in the lower third of the tibia. Her symptoms subsided spontaneously with symptomatic treatment and bed rest. Since this time she has been admitted twice with hemolytic crises. Study of the 9 available members of her family revealed the sickling trait in the patient's mother, brother, a maternal aunt and 2 maternal uncles, none of whom had anemia or history or physical findings suggestive of sickle cell anemia. Her maternal grandfather, an uncle, an aunt, and a cousin were found to be normal."

"None of the previously widely accepted theories fully explains the genetics in all reported cases. It is certain from study of reported cases and their families that transmission as a simple mendelian dominant is an impossible explanation in many instances. It is suggested that the homozygous-heterozygous theory is probably correct, but that failure of one or both parents of a sickle cell anemia patient to show sickling is the result of incomplete penetrance of the trait-producing gene. This explanation does not necessitate the assumption that much data previously accumulated are based on incorrect laboratory procedures."

Myocardial Infarction Simulating Angina Pectoris — STEIN, ISIDORE—*American Heart Journal*, 40: 325 (September) 1950.

"Although the clinical differentiation of angina pectoris and myocardial infarction has been placed on firm grounds, observations recently made encourage the belief that the usual criteria may in some instances lead to an erroneous diagnosis. It has been held basic that in the former, chest pain appears when increased stress is placed upon the cardiac musculature, while in cases of myocardial infarction there is pain in the chest at rest. Other well known points of difference are the duration and severity of the pain, the presence of fever, leukocytosis, and an elevated sedimentation rate, as well as the therapeutic measures (nitroglycerin, morphine, etc.) for relief. In angina pectoris the electro-

cardiogram appears normal or may reveal minimal to major aberrations. On the other hand, the progression of the electrocardiographic changes in myocardial infarction is a very important diagnostic consideration.

"In patients who have been subjected to attacks of angina pectoris for years, infarction of the myocardium may finally result. In these instances where there is an inadequate collateral circulation, the final obliteration of the lumen of the coronary vessels by atheromatous plaques eventuates in infarction. Infarction will also take place when the occlusive process occurs rapidly and without sufficient time for the anastomotic vessels to function.

"The following cases are reported wherein chest pain was present only on exertion (as with angina pectoris), but serial electrocardiograms demonstrated changes consistent with the diagnosis of myocardial infarction. These patients masquerading as victims of angina pectoris already had myocardial necrosis.

"Case Reports.—Case 1: L. W., a 58 year old white woman, in excellent health until two months before her present illness, stated that during this latter interval she noticed the onset of pain radiating across the chest on exertion, lasting a few minutes and subsiding promptly with rest. A week prior to her initial examination she experienced pain more severe and of longer duration while climbing a flight of subway stairs. After a half hour rest, she resumed her usual activities. No other symptoms of diminished cardiac reserve were presented other than some shortness of breath. The past history failed to reveal any blood pressure elevation.

"On physical examination no unusual cardiac findings were observed. The heart was not enlarged. The blood pressure was 170/100 mm. Hg. Fluoroscopic studies showed elongation of the aorta.

"The electrocardiogram was normal except for diphasic T waves in $CF_{4,\ 6}$. The diagnosis of angina pectoris was made and therapy instituted. During the following week the patient was ambulatory and without symptoms. No change in the cardiac findings was noted. The blood pressure at this time was 110/80 mm. Hg. The sedimentation rate was 22 mm. in one hour (normal, 10-15 mm. in one hour). The electrocardiogram now presented T wave inversions in leads I, CF_4, and CF_6. She was confined to bed for a five week period and made an uneventful recovery. At no time was any pain present while she was resting. The electrocardiogram returned to a normal configuration in five months. At present, two years after the onset of her illness, she is well except for occasional anterior chest pain on excitement or moderate exertion. The electrocardiogram has remained normal."

"Case 2: S. E., 20 years of age, while walking, suffered with severe precordial pressure lasting five minutes. There was an associated 'cold sweat.' Later on the same day, while playing ball, he had a recurrence of the same pain. This continued for several days following moderate effort. Pain was never present while he was at rest. Physical examination did not reveal any cardiac pathology. The initial electrocardiogram showed inversion of the T wave in leads I and $CF_{2,\ 4}$. One week later the same abnormalities were noted. Seven months later the electrocardiogram was normal."

"Case 3: S. S., a 52 year old salesman, had a 'pressing' pain in his anterior chest and a 'choking' sensation on physical exertion for about three years. A few weeks prior to admission his symptoms appeared after he had walked only two blocks. Blood pressure elevation was present for six months. He had no pain whatever at rest.

"On physical examination the findings were essentially as follows: The blood pressure was 170/100 mm. Hg. There was minimal enlargement of the left ventricle, but no congestive phenomena were found. An electrocardiogram showed inversion of the T wave in leads II, III, and $CF_{4,\ 5}$, and a significant Q_3.

"Because of the recent acceleration of his symptoms, he was hospitalized. During the three week period of bed rest he was entirely comfortable; however, the electrocardiograms and sedimentation rate studies (as high as 69 mm. per hour), etc., persisted in following the changing pattern typical of myocardial infarction. After six months the T wave in CF_4 was still inverted. The latter disappeared two months later."

"Case 4: P. L., 39 years of age, complained of substernal pain which appeared

on walking and with excitement for a two year period. In the few weeks prior to examination pain appeared upon less effort. His symptoms were never present while he was resting. There was no hypertension. No abnormal cardiac findings were observed on physical examination. The electrocardiogram showed significant Q waves and ST depression in leads I and $CF_{4,6}$; T waves in leads I and CF_6 were inverted. During six weeks in bed he remained symptom free, but the electrocardiographic changes were indicative of an anterior wall infarction. Sedimentation rates were as high as 50 mm. per hour. Eight months later, he was back at work, but he is subject to occasional, mild substernal pressure when overactive. The electrocardiogram has remained abnormal: T waves in leads I and $CF_{4,6}$ inverted, large Q waves in leads I and in $CF_{2,4,6}$."

"The importance of the early recognition of myocardial infarction is that with proper bed rest and sedation the demands on the heart are reduced until such time when the collateral circulation may become established, allowing for the healing of the ischemic portion of the myocardium. It is suggested that further investigation and serial electrocardiographs be made in patients having a history of angina pectoris with the appearance of (*a*) prolonged pain or (*b*) pain following less effort or (*c*) the absence or slowness of relief with nitroglycerin."

Aureomycin in the Treatment of Amebiasis — GUTCH, C. F.—*New England Journal of Medicine*, 243: 185 (August 3) 1950.

Twenty patients with proved amebiasis have been treated with aureomycin by the writer.

The 20 patients so treated presented the usual variety of symptoms and physical findings. "Four had suggestive impairment of liver function. Four others had narrowing or deformity of the cecum consistent with amebic typhlitis by x-ray study. No ulcerative lesions were demonstrable on proctosigmoidoscopy."

"Aureomycin was given orally in divided doses of 0.75 to 1.0 Gm. every six hours for a total of 8 to 28 Gm. The first patients treated received only 8 Gm. each. Later, the dosage was increased to 20 to 28 Gm., which has since been reduced, to determine, if possible, a minimum dosage level. Side effects were minimal, and in no case was it necessary to discontinue medication. Slight nausea, giddiness and headache increased in frequency as the total dose was increased. Slight pruritus ani developed in 2 patients four to six weeks after treatment.

"Symptomatic relief was prompt in all cases. All patients with initial roentgenologic changes in the colon were reexamined after six weeks, and disappearance of the deformity was found. Also, after completion of aureomycin therapy, the stool specimens did not contain macrophages, epithelial cells and cellular debris, which are frequently noted after other treatment.

"All patients had negative stool examinations at the termination of therapy. The examinations were repeatedly negative in 5 cases up to five months later and in 10 others three months after treatment. Two patients were found to have heavy infestations of trophozoites at their six week check-up. Both were given a second course, and in the first case five examinations of the stools up to two months later were negative. The more recent case had two negative series up to 10 days after the second course.

"What constitutes a proper follow-up period after any therapy for amebiasis depends upon the criterion taken for 'cure.' Most authorities require repeated negative stool examinations for 6 to 24 months." Review of cases treated at the writer's hospital previously indicated positive stools were most often found within three to five months of treatment, when recurrence took place. "Experience with other amebicidal agents (carbarsone, chiniofon, Vioform, Diodoquin and emetine) indicated a recurrence rate of 11.5 per cent within five months, the majority appearing within three months. Thus far, results of the aureomycin therapy appear to compare with best conventional treatment. Serious toxic effects of aureomycin are apparently minimal. No evidence of toxicity in the myocardium, marrow, liver or kidney was observed."

Pediatrics

First Case of Hemolytic Disease of the Newborn Due to Group ABO Incompatibility Alone, Successfully Treated by Transfusions of Blood Artificially Composed of Group O Red Cells and Group AB Plasma — SEIGNEURIN, R., ROGET, J., GROULADE, J. AND VIALLAT, F. — *La presse médicale,* 58: 939 (September 2) 1950.

At 5:00 P.M. on April 14, The Departmental Transfusion Center received three samples of blood coming from a newborn infant 30 hours old, his father and his mother. The infant weighed 6½ pounds and was normal at birth at 9:00 A.M. on April 13. There was 1 other normal child in the family. Jaundice appeared on the evening of the same day and became more pronounced during the next 24 hours. Although the spleen could not be palpated and the liver did not seem to be definitely increased in size, three samples of blood were sent to the Transfusion Center in order to detect any irregular agglutinins and to determine the Rh factor.

It is classical to consider an Rh incompatibility in these cases, the father usually being Rh+, the mother Rh− and the infant Rh+. The infant immunizes the mother during the course of intrauterine life and then there are usually found anti-Rh agglutinins in the mother's serum. These agglutinins increase during successive pregnancies and destroy the red cells of the infant.

However, in the present case, examination of the three bloods showed:

1. Father group B, Rh+; mother group O, Rh+; child group B, Rh+. Hence there was no Rh incompatibility.

2. No irregular agglutinins were found in the mother's serum. Her serum did not agglutinate any group O Rh+ or group O Rh− red cells in a lot of 12 samples of group O blood.

3. In view of these negative results, it was decided to determine the content of irregular agglutinins in the mother's serum. It is known that the serum of group O blood contains anti-A and anti-B agglutinins which usually titrate 1/64 and 1/6. However, it was found that her group O serum agglutinated up to 1/2,048 at 4° C. and 1/16 at 37° C. the group B red cells of the father or the group B red cells of another person. The red cells of group A were only agglutinated at 1/128 at 4° C. and at 1/16 at 37° C. Hence it could be concluded that the abnormally high content of anti-B agglutinins in the maternal blood resulted from immunization produced by the fetus who belonged to group B.

The child was then brought to the hospital as an emergency patient at 9:30 P.M. An examination of the blood was made at once and showed 3,360,000 red cells, 35,000 leukocytes, 14 per cent of erythroblasts, reticulocytosis, anisocytosis (5 to 14 microns) and polychromatophilia. A clinical examination showed frank generalized jaundice but the spleen could not be palpated and the liver did not seem to be increased in size. In spite of these negative findings, the presence of all the other signs (anemia, leukocytosis, erythroblastosis greater than 3 per cent, reticulosis, anisocytosis and jaundice beginning 6 to 12 hours after birth and increasing later) and the presence of abnormally developed anti-B agglutinins in the mother's blood, permitted making a diagnosis of hemolytic disease of the newborn due to group ABO incompatibility alone. Cases of this kind are rare in the medical literature.

The treatment used in this case is entirely new and permitted the infant to return home completely cured in 20 days. In the first place it was necessary to furnish the infant unagglutinable red cells capable of replacing those which had been lost and also capable of resisting the anti-B agglutinins coming from his mother. Red cells of group O fulfilled these conditions. But total blood of group O would contain anti-B agglutinins to which he was sensitized. Consequently it was necessary to use an artifice consisting of making a blood with equal parts of group O red cells and group AB plasma (plasma containing no agglutinins). This was done at once by placing 50 cc. of group AB plasma in a transfusion flask (plasma ob-

tained by decantation of group AB blood obtained 24 hours previously in an anticoagulant solution of citrate and glucose) and adding 50 cc. of red cells of the group O Rh+ (obtained from the sedimentation of group O Rh+ blood also obtained in an anticoagulant solution 24 hours previously). After moderate shaking to produce an homogeneous mixture of the red cells and plasma, on April 14 at 11:30 P.M. (38 hours after birth) the infant was given a transfusion of 100 cc. of this blood into a fontanel. This transfusion was given in 50 minutes and was supported perfectly. A second identical transfusion was given 18 hours later and a third was given on the twelfth day after a new decrease of the red cells.

The infant was then placed on artificial feeding. In fact, it was known that maternal agglutinins pass into the milk and this was confirmed because it was found that the maternal milk contained anti-B agglutinins at the same level (1/2,048) as in the serum. Hence it was necessary to discontinue breast feeding.

No other form of treatment was given. The jaundice decreased after the third day and disappeared on the ninth day. The erythroblastosis disappeared on the sixth day, the leukocytosis and anemia disappeared progressively and on the twentieth day the infant weighed about 7 pounds.

This case shows that in the presence of a grave jaundice of the newborn appearing within a few hours after birth and increasing later, it seems necessary to determine not only the Rh factor and sometimes the M and N factors and the irregular agglutinins of the mother's plasma but also the amount of the mother's regular agglutinins, especially if the mother is of the O group and the infant is of group A or B because the two incompatibilities may be superposed. The diagnosis of hemolytic disease of the newborn should, in addition, be based on an anemia of less than 4,000,000, a leukocytosis of over 15,000, an erythroblastosis of over 3 per cent and anisocytosis.

It is of value to determine the agglutinins of the maternal milk so as to discontinue breast feeding if agglutinins are passing into it.

A confirmation of the diagnosis of grave hemolytic anemia of the newborn requires an immediate specific treatment. The treatment used in the present case was a simple transfusion into a fontanel of 100 cc. of blood composed of group O red cells (Rh+ if the incompatibility is not due to the Rh factor or Rh− in the contrary case) suspended in group AB plasma.

Incidence of Subclinical Poliomyelitis in an Urban Area According to Age Groups — CASEY, ALBERT E., FISHBEIN, WILLIAM I., SCHABEL, F. M., JR. AND SMITH, H. T. — *American Journal of Public Health*, 40: 1241 (October) 1950.

"Field studies of poliomyelitis in Chicago, during 1945 and 1946, included investigation of contacts and noncontacts of infectious cases in 26 patient neighborhoods and parallel studies in an equal number of control neighborhoods located systematically 10 blocks north, south, east, or west of the patient neighborhoods (4 were 50 blocks distant)."

Stools were collected from 260 contact, noncontact, and control children. "From the stools, a total of 576 monkeys were inoculated."

"Characteristic histologic lesions including neurocytophagia, perivascular collars, focal necroses, and other reactions of monocytes and neutrophils were detected in the anterior or posterior horns of one or more levels of spinal cord and in the medulla of some of the 520 monkeys inoculated with stool specimens. (Following the inoculation, 56 monkeys died of trauma or of intercurrent conditions and a third monkey had to be substituted in each case, making a total of 576 animals actually used.) All histologic examinations were performed by the pathologist using the blind check method and duplicate slides cut on positive or doubtful cases for confirmation. A stool pool was considered positive if the characteristic lesions were encountered in one only of the two monkeys inoculated. The histologic lesions were found in each instance of observed paralysis or paresis in the monkey and, in a few instances, where no paresis had been observed.

"Poliomyelitis virus was recovered from the stool of 8 of the 104 children from the 26 control neighborhoods, from 54 of the 101 contact children, and from 6 of the 55 noncontact children residing in the

Table 1

Isolation of Poliomyelitis Virus from the Stools of Urban Children According to Age Distribution

Age in Years	Control Children						Contact Children						Noncontact Children					
	1945		1946		Total		1945		1946		Total		1945		1946		Total	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
0		1				1		2		1		3						
1	1	11		2	1	13	2		1	1	3	1		1		1		2
2	2	16	2	2	4	18	3	2	5	1	8	3		2		4		6
3	1	8		1	1	9	8	2	8	2	16	4		3		6		9
4	1	13		3	1	16	2	2	6	3	8	5	1	6	4	6	5	12
5		4				4	3	2	4	3	7	5				3		3
6		3		4		7	2	2		4	2	6				4		4
7		4				4	4	1		3	4	4		3	1		1	3
8		2		1		3		1		1		2				1		1
9		4		1		5	1			1	1	1		1		2		3
10	1	6		2	1	8	1	2			1	2				2		2
11		1				1	1	4		2	1	6		1				1
12		3				3	1	1	1		2	1		1				1
13							1				1							
14		1				1				1		1				1		1
15		1				1		1				1		1				1
16		1				1												
17								1				1						
18		1				1												
26										1		1						
Total	6	80	2	16	8	96	29	23	25	24	54	47	1	19	5	30	6	49

patient neighborhoods during 1945 and 1946." These have been distributed according to year and to age of the child (table 1).

"Of the 8 positive control children, 6 came from the 1945 and 2 from the 1946 study. The stool inoculum from the 2 positive children in the 1946 study caused paralysis and characteristic lesions in both monkeys. The 6 positive children in the 1945 study came from four neighborhoods. In the two neighborhoods in 1945 having only 1 positive child, the diagnosis rested on characteristic histologic lesions in one monkey only. Fever or symptoms compatible with subclinical poliomyelitis were noted in each child; and in one instance both monkeys inoculated with specimens from the child had a fever.

"Of the 6 positive noncontact children 1 was from 1945 and 5 from four different neighborhoods in 1946. Both monkeys were positive in stools from 1 of the 6 children; paralysis and/or fever was noted in each of the single positive monkeys and symptoms or fever compatible with subclinical poliomyelitis among 4 of the 6 children.

"Thus, of the 14 positive noncontact or control children, both monkeys were positive in only 3 instances, possibly indicating minimal amounts of stool virus in the inoculum. Thus, at least 2 monkeys and the triple inoculation method and careful histologic examinations are indicated in sampling studies of controls and noncontacts. Only 9 of the 14 noncontacts and control children had observed symptoms or fever compatible with subclinical poliomyelitis during the 2 week observation period.

"Discussion.—The poliomyelitis incidence of 11 per cent among the noncontacts in the patient neighborhoods was within the limits of sampling error of the poliomyelitis incidence of 8 per cent observed among the control children residing in neighborhoods 10 blocks distant. Because some neighborhood histories were undoubtedly incomplete, an incorrect classification of some noncontacts might explain the 3 per cent difference, when not due to sampling alone. Nevertheless, the viral data support conclusions . . . . that the high incidence of poliomyelitis among the known contacts of infectious paralytic cases was due largely to person to person transmission of the virus. The data formerly or herein presented offer no direct information as to whether the widespread subclinical disease among the control and noncontact

children was transmitted by person to person contact or by some other means (insect or otherwise).

"It may be that poliomyelitis infection in the families of paralytic patients represents instances of overwhelming virus contact (or challenge) and as such may bear little relation to the epidemiologic or immunologic conditions in the control neighborhoods and among nonfamilial contacts, Thus hypotheses based on such observations may have an inherent fallacy.

"In the Chicago studies, care was taken that the large proportion of the contacts were nonfamilial; thus, 18 were familial (brothers, sisters, parents, children) and 83 were nonfamilial. Of the 10 familial contacts, 1-5 years of age, 8 were positive, and 38 of the 49 nonfamilial contacts were positive. However, among 8 familial contacts, 6 years of age and older, 6 were positive, whereas only 7 among 30 nonfamilial contacts of similar age were positive. A low virus recovery rate among nonfamilial contacts 6 years of age and older may be characteristic of an urban population subjected to normal virus challenge." A similar age trend may be noted among the controls and the noncontacts (table 1).

"Between July 24 and August 18, inclusive, and between September 19 and November 3, inclusive, during 1945 and 1946, the entire stool collections on 50 of the control children were made. The pooled specimens from 2 of the children were positive (4 per cent). Since the stools were from periods separated 1-3½ months apart, it may be presumed that, if stools had been collected on the children examined between July 24 and August 18, inclusive, during September 19 to November 3, and vice versa, those collected between September 19 and November 3, examined between July 24 and August 18, the yield would also have been 2 positives but different children from those observed. Consequently, the actual positives on the 50 children were probably 4 during these collection periods in a single year, or 8 per cent.

"Between August 19 and September 18, inclusive, the stool specimens on the remaining 54 children were partially or completely collected. There were 6 positives, or 11.1 per cent. This period corresponds with the highest incidence of the clinically reported disease in Chicago during 1945 and 1946 (380 of the 994 reported cases). Presumably, if the 54 children had been examined between July 24 and August 18, and between September 19 and November 3, respectively, 8 per cent different children (4.3) might have had recoverable virus in the stools, and, likewise, had the other 50 children been examined between August 19 and September 18, some additional 11 per cent, or 5.5 children, might have had recoverable virus. Thus, some 20 (19.8) of the 104 children probably had recoverable stool virus in a single year. Of the 994 clinical cases of poliomyelitis reported in Chicago during 1945 and 1946, some 884 (85 per cent) occurred during the period of stool collections. An additional 15 per cent of the total subclinical cases may well have occurred during the period from January 1 to July 24, and November 3 to December 31. This was probably offset, however, by overlapping during the collection period, since between the fourth and eighth weeks after onset in the subclinical and clinical disease, virus may be recovered in about 15 per cent.

"When stools were collected on the day of or on one day prior to onset in 83 cases of subclinical poliomyelitis, virus recovery was 83 per cent and 94 per cent respectively; but for the period between 1 week prior to 3 weeks after onset of the first fever or symptom compatible with subclinical poliomyelitis, the virus recovery was 63 per cent."

"It was calculated that most children in Chicago had probably had poliomyelitis once by the fourth birthday, and 75 per cent perhaps twice by the sixth birthday, either different strains or reinfection. From these calculations it would appear that on the average over 100,000 to 125,000 cases of poliomyelitis occur in Chicago each year, or 3-4 per cent of the total population.

"Paralysis in poliomyelitis representing a condition occurring less than once in each 200 cases may be a reinfection in sensitized individuals, or in individuals with poor natural or acquired resistance." Repeated paralytic disease, sometimes fatal, has been encountered in field work, and the low antibody titer after paralytic disease may not always be due to strain

differences. "The significantly increased incidence of residual paralyses in clinical cases over 7 years of age may represent a constitutional reaction to delayed contact with a strain of virus usually encountered during the preschool period, as well as to possible sensitization from prior infection.

"The mode of transmission of poliomyelitis among the 159 controls and noncontacts was not directly established. However 9 of the 14 from whom virus was recovered were known to have had fever or symptoms compatible with subclinical poliomyelitis.. At least 94 per cent of such cases had recoverable virus in the stool on the day prior to onset in a quantity comparable with that in the clinical or paralytic disease. In addition, 5 of the 14 had fever and two or more symptoms compatible with poliomyelitis including headache, leg or neck ache, sore throat, etc. Current work has shown that almost 100 per cent of such children have virus in the throat as well as in the stool on the day prior to onset. In terms of the epidemiology of the disease this would indicate that annually in Chicago during the summer and fall some 40,000 children have virus in the throat and in the stool on the day before onset in a quantity comparable to that found on a similar day in the clinical or paralytic disease and at least an additional 32,000 children have virus in the stool but not in the throat on the day prior to onset. Ninety per cent of this great reservoir of the disease is represented by the ambulatory preschool child 1-5 years of age who probably brings poliomyelitis home to his parents and older brothers and sisters rather than vice versa. The child with throat and stool virus need on the average infect only 3 others to account for all of the estimated poliomyelitis. Neighborhood studies have proved that such a type of spread actually takes place."

Seasonal Distribution of Poliomyelitis — ARMSTRONG, CHARLES — *American Journal of Public Health*, 40: 1296 (October) 1950.

"There are certain epidemiological features of poliomyelitis which have been so frequently and so generally observed that they are recognized as characteristics of the disease. One such characteristic is a tendency for the seasonal variation of poliomyelitis to be slight in the tropics, with a tendency for outbreaks to be confined to the warm months of the year as one proceeds either north or south from the equator." It is this epidemiological feature of the disease which will be here discussed.

Means of Transmission. — "Contact, arthropods, food, and water are all recognized as possible means for the transmission of poliomyelitis. . . . While it must be admitted that occasional cases may be acquired by each of these methods, the evidence . . . . is overwhelming in indicating contact as the one common means of transmission, especially such close personal contacts as occur within a household."

One is therefore confronted with the difficulty of explaining why poliomyelitis, a disease transmitted by close contact, should be most prevalent in that portion of the year when people spend most of their time in the open and why it should tend to wane rapidly when cool weather induces people to congregate indoors in search of warmth, a behavior quite in contrast to other contagious diseases such as diphtheria, measles, etc. "Several theories have been suggested in an effort to explain this anomaly of poliomyelitis outbreaks."

The possible explanation for the seasonal variation of poliomyelitis which will be here considered is that the usual portal of effective entrance for the virus of poliomyelitis in man may tend to be more permeable during warm weather than in cold.

"Portal of Entrance and Seasonal Incidence of Poliomyelitis.—The assumption that the seasonal incidence of poliomyelitis depends upon variations in the permeability of the usual portal of entry for the virus does not require the assumption of any extra human source of multiplication for the virus or of any seasonal alteration in the basic resistance of the population, or any seasonal variation in the infectivity of the virus." It does, on the other hand, relate the observed seasonal variation to an external mechanism more directly in contact with variable seasonal factors of environment—factors which are capable of producing observable alterations. "For instance, it is a rather general experience that nasal and throat secretions tend to be more copious in cool weather after fires

have been started than is the case in warmer portions of the year and upper respiratory infections tend to be more prevalent."

Specific Antibodies in Nasopharyngeal Secretions.—Several authors demonstrated the presence of specific antibodies against poliomyelitis virus in the nasal secretions of a portion of the persons examined, and also demonstrated that the content of antibodies in the secretions tended to vary with the content of antibodies in the serum, but at a lower level. The author has recently demonstrated that nasal washings taken on the same individual when the mucous membranes were quiescent, and when stimulated to secretion by an experimentally induced upper respiratory inoculation, showed a higher content of antibodies in the latter washing, indicating that the antibody content persisted with the induced secretion and was not simply diluted by it. "In winter, the breathing of cool air of low humidity would tend to concentrate existing secretions through drying. Thus, it is conceivable that some persons who might upon exposure become victims or carriers of the virus in summer would tend to spread no virus or a neutralized one in winter."

The problem considered here would appear to be largely concerned with persons in whom specific antibodies are lacking.

Nasopharyngeal Secretions of Nonimmune Persons.—The normal mucous secretions long have been considered to be a protective mechanism and are present throughout the respiratory and alimentary tracts. "Considering either location as a possible portal of entry, the upper respiratory tract appears to be more directly exposed to climatic variations than is the alimentary tract. To this extent, the concept under consideration would appear to favor the nasopharynx as the more probable portal of entry and of exit for the virus effective in the spread of poliomyelitis. This possibility is supported by the fact that the virus has been frequently demonstrated in the throat for a few days before to a few days after onset of symptoms, a period which has, on epidemiological grounds, come to be considered as the infectious period of the disease.

"The occurrence of poliomyelitis following tonsillectomy, and certain experimental evidence also support the nasopharynx as a possible portal of entry for the virus."

Nonspecific Action of Mucin.—Several authors demonstrated that certain bacteria, harmless to experimental animals, when injected intraperitoneally in ordinary diluents became rapidly lethal when 5 per cent of gastric mucin was incorporated with the same dose of organisms.

"Various explanations for this observed fact have been suggested, the simplest of which is that mucin acts by coating the bacterial cells and possibly the peritoneal cells as well, so that the organisms are protected from the animal's cellular and perhaps other defense mechanisms while remaining in an environment suitable for their multiplication.

"Now, if this simple explanation be wholly or in part correct for bacteria, it appears that the effect might be reversed in case of a virus, which must come in close contact with and enter a susceptible cell before multiplication can occur. The avidity with which a mucin containing solution clings to dry glassware and its facility for plugging siliceous filters suggests that mucin might hold in addition an attraction for negatively-charged virus particles.

"Certain it is that poliomyelitis reaches its highest incidence in temperate climates when upper respiratory infections are at their lowest ebb and secretions from the membranes are tending toward a minimum. Whether the nasopharyngeal secretions have any such action as suggested or not, the presence of an abundant secretion on a surface would certainly tend to dilute and to carry away any accompanying virus."

The author now considers the upper respiratory passages when such natural irritants as cold, drying or upper respiratory infections tend to stimulate secretions. "In cold weather the atmosphere, whether warmed artificially or by inspiration, suffers a drop in relative humidity with a corresponding tendency to take up moisture and thus to stimulate normal membranes to additional secretion, which secretions tend to be concentrated through drying while common upper respiratory infections show a tendency to develop.

"In warm weather the temperature of the atmosphere and its relative humidity are less altered by inspiration and as com-

monly observed, upper respiratory secretions and common infections are at a minimum while poliomyelitis tends to reach its greatest prevalence.

"Atmospheric temperature in cold weather is far more subject to artificial regulation than is humidity; therefore, it might seem possible that under actual conditions of living as in the United States, atmospheric humidity is more important in influencing susceptibility to exposure than is temperature.

"There is, however, a striking correlation between seasonal (summer) temperatures and the occurrence of poliomyelitis as noted in temperate climates; the correlation with atmospheric humidity is, however, less apparent. In so far as atmospheric variations may directly affect the respiratory membranes, it is evident that it is the conditions of the air within the respiratory tract and not at some weather station, that are of significance." One must, therefore, take into consideration the effect of warming the atmospheric air to the temperature of air within the respiratory passages. "The expired air is always at a temperature of about 90° F. and 90 per cent saturated with moisture. It is therefore the difference between the absolute humidity of inspired air and the absolute humidity of 90 per cent saturated air at about 90° which measures drying effects on the mucous membranes. A striking correlation between absolute humidity and the incidence of poliomyelitis is clearly apparent."

Susceptibility to Infection.—The author's concept attempts to relate the summer prevalence of poliomyelitis, the development of immunity, and the regeneration of virus to the conditions which prevail at a portal of entrance and of exit for the virus, but it has nothing to do with whether effectively exposed nonimmune individuals develop recognizable symptoms or simply immunity—such considerations being related to natural resistance as it relates to age, sex, overexertion, and perhaps other factors rather than to the permeability of a portal of entry.

"If this simple concept is operative, it is necessary, however, to assume that it acts differently in poliomyelitis from in measles, mumps, chickenpox, smallpox, or influenza which tend toward a cool weather prevalence. This difference does not appear entirely illogical, however, since poliomyelitis virus induces recognizable symptoms by reaching susceptible cells of the central nervous system by way of nerve fibers and tracts and has no demonstrated attraction for surface cells and no demonstrated synergistic action with bacteria. The other viruses mentioned, however, are capable of parasitizing surface cells and have in some instances an attraction for certain available cells as revealed by the red cell agglutination phenomenon or a possible synergistic action with some types of the varying but ever present bacterial flora of the respiratory tract. Under such circumstances, it appears possible that the opportunities for infection to pass from one person to the next are more important in the case of those infections showing winter prevalence than are the local conditions at the virus implanted area." If the concept under consideration is, however, effective in poliomyelitis, one should expect the closer person to person contacts of winter to be relatively ineffective due to the relatively greater scarcity of virus during the cool portions of the year."

Local responses to infection are generally considered to be defensive in nature and there is indication that certain bacteria or their products may exert a hindering effect upon certain virus infections such as vaccinia, and mouse pneumonia.

"Recently a number of therapeutic agents have come into common use in the United States which exert an inhibitory effect upon several types of organisms commonly present in the upper respiratory passages. It is therefore interesting to speculate upon the possible relationship of their employment to the high incidence of poliomyelitis reported in the United States for 1948-1949 and 1950 to date.

"The usual and apparently logical explanation for this situation is that it is due to the more frequent reporting of mild illnesses as poliomyelitis." This could readily explain why deaths have not risen in number as have the reported cases; however, this explanation is not conclusive since one is ignorant as to what has been accomplished, if anything, either in the treatment or prevention of the fatal types of poliomyelitis.

Hepatitis and Typhoid Fever — Gómez Orozco, Luis — *Boletín médico del Hospital infantil*, 7: 547 (August) 1950.

The author reports the case of a boy, aged 2, with a noncontributory family history and a personal history of alimentary deficiency and whooping cough. Two weeks before admission the boy developed fever, apparently of a continuous type, with predominance of the evening hours, associated with headache, anorexia and constipation; the latter had subsided before admission. Examination revealed impairment of the nutritional condition, a saburral tongue, reddening of the pharynx, scanty bronchial stertors over both lungs, a globular tympanitic abdomen, a tender liver, reaching 3 cm. below the costal margin, and petechiae at the level of the abdomen and the anterior surface of the chest. The agglutination test for typhoid fever proved positive in a dilution of 1:500, and typhoid fever bacilli were obtained on two blood cultures. The blood picture showed discrete neutrophilia and toxic granulations in the neutrophils. Only the first of four stool cultures showed typhoid fever bacilli. The serologic reactions for syphilis and the Mantoux test were negative. On the day after admission the hepatomegaly was no longer demonstrable but jaundice had appeared. The urine contained bile salts, scanty erythrocytes, pyocytes, granular casts, and traces of albumin. The thymol turbidity and the cephalin cholesterol function tests of the liver proved positive. The jaundice diminished after four days and subsided completely after nine days. Sulfadiazine was given because of pharyngeal reddening and another blood picture showed moderate hypochromic anemia and leukopenia; bleeding, coagulation, and prothrombin time were normal and urinalysis was negative at that time. The van den Bergh reaction was positive for both direct and indirect bilirubin, the cholesterol level was 133 mg. per cent, the total protein level was low and the albumin-globulin ratio was inverted. The alpha globulin fraction amounted to 0.87, the beta fraction to 1.16 and the gamma fraction to 1.59 per cent. A puncture biopsy of the liver was carried out and showed intense alterations of the liver structure, including congestion with marked leukocytosis in the sinusoids without intense foci of infiltration, degenerative phenomena of the liver cells apparently with predominance of the center of the lobules and characterized by cloudy degeneration, protoplasmatic swelling and slight retention of bile pigment, and marked fatty metamorphosis with perilobular predomination; focal necrosis and fibrosis were not demonstrable. The anatomic diagnosis was discrete hepatitis with marked fatty metamorphosis. The histologic picture was not typical of the hepatitis of typhoid fever but was not incompatible with it.

The urinary urobilinogen reaction was negative. The liver function tests were repeated after 10 days and were unchanged; the bromsulphthalein test showed 10 per cent after 30 minutes and 5 per cent after 60 minutes. The prothrombin percentage was 70 and rose to 80, 24 hours after administration of 1 mg. of vitamin K.

After the second day of his hospital stay, the patient was afebrile. The stools were not acholic. A hepatocellular jaundice was definitely dealt with, and hemolytic or obstructive jaundice could be ruled out. The question arose whether the jaundice was caused by the typhoid fever which had almost subsided and which rarely causes jaundice, or by a virus, with development in a patient with typhoid fever. The fever subsided at the very moment when the jaundice appeared; the latter showed a short benign course which seems more compatible with virus hepatitis. According to Popper transitory biliary obstruction is present in 12 per cent of the cases of virus hepatitis and 33 per cent of the cases of toxic hepatitis. The thymol flocculation and the cephalin cholesterol tests were intensely positive and this occurs most frequently in virus hepatitis according to Popper. The tests were positive on two occasions when the patient was afebrile, excluding an infectious condition as source of error. Inversion of the albumin-globulin ratio is more frequent in toxic than in virus hepatitis but only slightly so. The increase of the gamma globulins during convalescence has been reported in virus hepatitis. The total cholesterol level was somewhat low and this has been reported more frequently in virus than in toxic

hepatitis. The slight cellular infiltration and the predominantly centrilobular cloudy degeneration of the liver cells as found in the case under consideration have been reported by Popper in virus hepatitis, but fatty metamorphosis of the perilobar cells as encountered in toxic hepatitis and in malnutrition were also encountered, and the patient suffered from malnutrition. The laboratory data are not sufficient to elucidate the etiology of the hepatitis in this case, but the clinical course suggests virus hepatitis, developed in a patient with typhoid fever.

Human Hyperimmune Serum and Streptomycin as Treatment of Whooping Cough in Infants and Small Children — HATZ, F. AND BURCKHARDT, C. — *Annales paediatrici*, 175: 274 (September) 1950.

It has been reported that a marked influence on the course of whooping cough in infants can be obtained with streptomycin treatment and that the mortality which had amounted to 75 per cent before is considerably reduced. Several authors have confirmed these results. The dosages ranged between 40 and 50 mg. per Kg. body weight, the streptomycin was injected intramuscularly at intervals of four to six hours, and the average period of treatment amounted from 7 to 14 days.

Recently, treatment of whooping cough has been expanded, and human or animal hyperimmune serum has been used, alone or in association with streptomycin. Progress has been achieved with this method, particularly in whooping cough of infants with its frequently life-threatening complications. In one set of statistics on 565 cases of infants and small children the mortality was 1.8 per cent, as compared to a mortality of 5 per cent in a control series. All authors stress that treatment with hyperimmune serum should be started as early as possible in infants and in seriously sick small children.

Recently, treatment of whooping cough with streptomycin inhalation, with or without associated streptomycin injections, was tried in older children. With respect to the inhalation, the *p*H of the sputum may be of significance, but no definite evaluation of this method is as yet possible. In the authors' opinion it is not suitable for infants and small children. Aureomycin and chloromycetin are also said to have a favorable influence on whooping cough and its complications.

Since 1948 the authors have treated whooping cough with streptomycin, alone or in association with human hyperimmune serum. As evaluation of the effects in children above the age of 2 is made difficult by the milder course and the increasing participation of psychic factors, a comparison was made between 50 children below the age of 2, half of whom were treated with streptomycin and the other half with streptomycin and hyperimmune serum, and 50 children of the same age group who had been treated chiefly with vitamin C during the two year period before 1948. The effects of treatment were evaluated on the basis of the average daily number of attacks per week of treatment.

The diagnosis was based on epidemiologic data, history, and clinical picture including hematologic data, while bacteriologic and serologic methods were not resorted to. All patients were admitted in the convulsive stage and the attacks were registered day and night by the nurses. The blood picture showed in all cases definite leukocytosis with relative lymphocytosis and the chest plate was characteristic in most cases. Complications included bronchitis, bronchopneumonia, encephalitis, and in infants dyspepsias and severe vomiting; but all complications were already present on admission and none developed during the hospital stay. Of the earlier control group of 50 children below the age of 2, 45 had been treated with vitamin C and 5 with an antihistaminic, and supplementary treatment had included belladenal, "ipedrin," sulfonamides for bronchitis and bronchopneumonia, inhalations, stimulants, oxygen, spinal puncture, chloral hydrate rectally and luminal for encephalitis, and dietary measures for dyspepsia. Complications in this group included 1 case of encephalitis, 5 each of bronchopneumonia and bronchitis, 12 of severe vomiting, and 7 of associated dyspepsia. Five of the children had been vaccinated with a mixed vaccine before admission. In most cases the number of attacks decreased only slowly during the first weeks and sometimes even still increased, and their severity decreased only slowly. General con-

dition and appetite were always impaired during the first two weeks. The average number of daily attacks was eight during the first week and four during the fifth week, and in the presence of complications the number often did not decrease until the fourth week. There were no deaths.

The 25 cases of combined hyperimmune serum and streptomycin treatment included 17 infants below the age of 6 months. Cutter's "hypertussis" was used, containing in 2.5 cc. of serum the gamma globulins from 20 cc. of serum of healthy adults who had been actively immunized with hyperconcentrated whooping cough vaccine phase I and who had a history of whooping cough. One ampul of 2.5 cc. was given intragluteally daily for the first three days after admission. Streptomycin and dihydrostreptomycin were each used in half the cases, in a dosage of 50 mg. per Kg. body weight daily, divided into three intramuscular injections; the antibiotic was continued for four weeks unless the attacks stopped earlier. The maximal daily dose was 900 mg. Additional treatment for complications was the same as in the control group except that the sulfonamide was replaced by penicillin (100,000 units twice daily) in the presence of increased vomiting; in dyspepsia penicillin was given systematically as additional treatment in the form of four injections of 40,000 to 60,000 units daily. Complications in this group included 2 cases of encephalitis, 1 of bronchopneumonia, 5 of bronchitis, 4 of severe vomiting, and 2 of associated dyspepsia. One patient had been vaccinated with mixed vaccine before admission. In 23 of the 25 cases the number and severity of the attacks began to decrease appreciably and progressively within a few days after institution of treatment, and general condition and appetite improved at the same time; improvement was sometimes sudden in young infants. The average number of attacks per day was 10.7 during the first and 1.9 during the fifth week. Even in the presence of complications the number and severity of the attacks decreased after the first week, and the complications improved rapidly. There were no deaths. The number of cases treated with hyperimmune serum alone is not large enough to permit any definite conclusions. The combined hyperimmune serum and streptomycin treatment is recommended by the authors for young infants and, in the presence of severe complications, for small children as well.

The 25 cases below the age of 2 treated with streptomycin or dihydrostreptomycin alone included 9 infants below the age of 1. Supportive treatment was the same as in the former group. Complications included 1 case of bronchopneumonia, 5 of bronchitis, 1 of severe vomiting, and 3 of dyspepsia, while encephalitis did not occur. No child had been vaccinated with mixed vaccine before admission. The decrease in number and severity of the attacks was less prompt in most cases than with the combined serum and antibiotic treatment, and a definite decrease often supervened only towards the end of the second week. General condition and appetite improved in all cases within the first week. No difference could be established between the effect of streptomycin and dihydrostreptomycin. The average daily number of attacks was 8 during the first and 1.2 during the fifth week. The decrease in number and severity of the attacks was the same in uncomplicated and complicated cases, and the complications improved rapidly. There were no deaths.

In intercurrent grippal infections a slight increase in the number of attacks was observed in some cases in spite of continued streptomycin treatment, regressing with control of the infection.

Six of the children treated with streptomycin alone or in combination with serum (corresponding to 12 per cent) developed a rash as a side effect; this rash resembled either German measles or scarlet fever. On appearance of such a rash the antibiotic was always temporarily discontinued, and the attacks always rapidly increased in number and diminished again when streptomycin treatment was resumed, with half the usual dosage on the first day. The rash lasted four to eight days. Other side effects of streptomycin, like eosinophilia, conjunctivitis, asthmatic conditions, and disturbances of the eighth nerve were not observed, due to the short period of treatment and the lesser toxicity of dihydrostreptomycin.

Since conclusion of this report another 10 cases have been treated with the same success, but there was 1 death in an infant

aged 8 weeks, with severe dystrophy and bilateral suppurative bronchopneumonia.

In children above the age of 2 streptomycin was used in the same dosage and for the same length of time, and definite shortening of the disease was observed; but the effect was not as conclusive as in the younger age group.

Vitamin D Intoxication in a Child with Rheumatoid Arthritis — HYDE, JOHN S. AND RICHMOND, JULIUS B.—*American Journal of Diseases of Children*, 80: 379 (September) 1950.

"Harmful and lethal effects resulting from the prolonged administration of large doses of vitamin D used in the treatment of arthritis in adults are well established." The administration of high potency vitamin D in the treatment of rheumatoid arthritis in a child resulting in soft tissue calcification and renal insufficiency, has not been previously reported. These findings in a patient under the writers' observation prompted this case report and discussion.

Case Report.—G. G., a 12 year old white girl, was admitted to the hospital on May 25, 1949, because of painless abdominal enlargement of one month's duration.

"The past history revealed that she had 'scarlet fever' at 6 months of age, from which recovery was uneventful. When the child was 17 months of age, the mother noted that she began to limp and was unable to move the right knee through a full range of motion. At 18 months the child had a rash, which again was considered to be 'scarlet fever.' The right knee continued to be the only joint manifesting symptoms until she reached 4 years of age, when within several weeks pain, swelling and limitation of motion of the joints of the hands and feet developed. Pain and limitation of motion of the spine, particularly in the cervical region, developed. The appetite became poor, and gain in weight was slow. The joint deformities gradually became more pronounced, and weakness and easy fatigability developed." High potency vitamin D capsules were given in doses of 2 to 3 capsules (100,000 to 150,000 U.S.P. units) orally each day from the development of multiple joint symptoms at 4 years of age to the time of her first admission to the hospital, on March 10, 1947. "This was a total of five and one-half years of therapy.

"Within a few days after the start of therapy, the mother noticed that the child had definitely increased thirst: She asked for a large glass of water at bedtime, a request which she had never made before. Soon she began to awaken once or twice during each night to urinate and to drink more water. Since then she has required about 8 large glasses of water daily. Three weeks after vitamin D therapy was begun, she was relieved of her pain. Whereas previously she was flat on her back in bed with pain, she was then able to get up and go to the toilet by herself for the first time in months. At this time, anorexia developed, and she vomited several times a week. Appetite for sweet foods was lost. She never liked milk, but she drank about 2 glasses a day. She failed to gain weight while receiving vitamin D therapy, weighing about 33 pounds (15 Kg.) for 5 years. Her skin became dry and pruritic. Stupor was not noted except for delirium of two days' duration during an episode of pneumonia in March 1945. Sulfonamides were used sparingly because it was recognized that her kidneys had poor function. Attacks of pain, swelling and stiffness in joints continued to occur after infections of the upper respiratory tract.

"The family history revealed that the father died of heart trouble in September 1946. The mother, aged 41, was living and well. There were three brothers, aged 13 years, 7 years and 4 months, all in good health. The patient had been immunized against diphtheria but had not had a vaccination for smallpox."

She was first seen when she was admitted to the hospital, March 10, 1947, because of pain, swelling and deformity of numerous joints. "Physical examination of the child at that time revealed that she was thin and undersized, with multiple joint deformities. Her weight was 33 pounds, and her height was 45 inches (114.3 cm.); both measurements ranked her below the 3 percentile group for her age (Stuart-Meredith charts). The head tilted to the right but could be moved to the left. The cardiac and pulmonary findings were normal. Blood pressure was 98 diastolic and 70 systolic. The spleen was palpable 5

cm. below the left costal margin and was firm. The liver was not palpable. The extremities were very thin; marked muscular atrophy was observed. There was fusiform swelling of all the joints of the fingers; moderate swelling about the ankles, knees and wrists, with considerable limitation of motion of these joints, was observed. The patient walked with a shuffling gait consisting of very short steps. All the mandibular movements were possible with only slight restriction of range."

"The roentgenograms indicated narrowing of the joint spaces of the knees, with marked calcification of the popliteal arteries. The lateral aspects of the femoral and tibial epiphyses were irregular in contour, with some soft tissue calcification about the knee. There was moderate soft tissue swelling about the joints. The cervical portion of the spine demonstrated irregular calcification and contour. Roentgenograms of the hands and wrists revealed distortion of the distal portions of the ulna and radius, moderate destruction and deformity of the carpal bones, thinning and irregularity of the epiphyses of the proximal phalanges and marked loss of calcific density throughout all the bones of the hands and forearms. Laminagrams of the temporomandibular joints revealed marked decrease in excursion of the condyles, although the degree of opening appeared adequate. The condylar heads were flattened and irregular, more on the left than on the right. The joint spaces appeared to be narrowed. Plain roentgenograms of the abdomen showed calcification of the aorta and of the iliac and femoral arteries. Intravenous pyelography disclosed marked delay in the appearance of the dye, with a suggestion of early caliectasis on the right. The roentgenograms of the chest showed marked increase in bronchovascular shadow on the right with pleural adhesions medially. The cardiac shadow was normal.

"Her progress in the hospital was marked by a recurrent low grade febrile course. The use of vitamin D was discontinued on admission. Physical therapy was given to increase motion of the joints. Transient swelling of the right temporomandibular joint occurred, and she complained of occasional pains in the heels. Excessive thirst and nocturia were noted. She weighed 35½ pounds (16.1 Kg.) on discharge, July 22, 1947.

"After the patient's discharge, there was no recurrence of arthralgia. Stiffness of joints and irritability were present in the early morning. As the day progressed, the 'joints would loosen up and she became her normal cheery self.' She was unable to extend the arms completely or to stoop over. She continued to walk with a shuffling gait.

"During November 1947, she had pneumonia, which responded satisfactorily after eight days of penicillin therapy. She was seen at infrequent intervals by the family physician. In April 1949, a check-up examination revealed a 4+ reaction for albumin in the urine. Two weeks later, she complained of a sore throat and had a temperature of 102 F. for four days. During this time the abdomen began to enlarge. The child's slacks were 'let out' to adjust to her increasing abdominal circumference. She gained 3 pounds (1.3 Kg.) in two weeks. She had no edema of the extremities or eyelids.

"Her appetite was fair. She did not have vitamin supplements after her return home. Excessive thirst and polyuria continued, and nocturia persisted despite the discontinuance of vitamin D therapy.

"Physical examination on May 25, 1949 showed the continued presence of emaciation and multiple skeletal deformities in this 12 year old girl. She was cooperative and cheerful. Her temperature was 99.4 F., weight 46 pounds (20.9 Kg.) and height 52½ inches (133 cm.). Her blood pressure was 168 systolic and 114 diastolic. The skin was dry. There was mild generalized lymphadenopathy. Several carious teeth were noted. The heart and lungs were normal. Slight shifting dulness and a minimal fluid wave were noted in the moderately protuberant abdomen. The liver was palpable 2 cm. below the right costal margin. The spleen was felt 4 cm. below the left costal margin. The genitalia were those of an immature female, with scanty pubic hair.

"There was full flexion at the elbows, but extension was limited to 160 degrees bilaterally. Flexion of the fingers was moderately restricted. The phalangeal, metacarpophalangeal and wrist joints presented knobby enlargement bilaterally. The

knee joints had complete range of motion. There was bilateral hallux valgus with marked adduction of the great toes. No edema was detected. Reflexes were equal and hyperactive.

"Ophthalmologic examination with the slit lamp revealed a whitish ring of opacification along the limbus of the cornea bilaterally. It appeared to lie superficially, mostly in Bowman's zone, and was limited to the interpalpebral area both temporally and nasally. There were numerous small calcareous deposits in the bulbar conjunctivas and also in the interpalpebral zones. Funduscopic study showed the margins of the disks to be mildly blurred and the vessels slightly arched over the margins. The vessels presented variation in the caliber of the arterioles with tortuosity and dipping, arteriovenous compression and disproportion (1:3). Vision was 20/17, bilateral and uncorrected. These findings were interpreted to be grade II hypertensive retinopathy and calcareous deposition in the corneas and conjunctivas, probably representing further evidence of hypervitaminosis D.

"Roentgenograms of the cervical portion of the spine showed the vertebral bodies to be abnormally straightened; a roentgenogram of the chest revealed a moderate obstructive emphysema of the left lung for which bronchoscopy could demonstrate no definite cause, and arthritic changes of the shoulder joints were observed. A roentgenogram of the abdomen demonstrated enlargement of the spleen, calcification of the abdominal aorta, renal, iliac and femoral arteries and sclerosis of the acetabular margins with loss of joint space in both hips. Lateral views of the knees in flexion revealed calcified vascular shadows in the popliteal fossae. The bones were demineralized, the joint spaces decreased and the joint surfaces were irregular; views of the hands showed spotty demineralization throughout with loss of joint space and destruction of joint surfaces and bony substances in the region of the joints. A barium swallow revealed no esophageal varices."

"The patient continued to be free of pain. Nocturia was especially notable. The abdominal enlargement remained unchanged, but peripheral edema was not observed. On repeated examinations her blood pressure was shown to range between 176 systolic and 114 diastolic and 190 systolic and 130 diastolic. The venous pressure was 110 mm. of water in the antecubital vein. The child remained afebrile; she was permitted unlimited activity and was discharged June 11, 1949."

Typical symptoms observed are anorexia, nausea and vomiting, excessive thirst associated with polyuria and constipation alternating with diarrhea. Other features noted are headache and pain in the abdomen, back and extremities, associated with stiffness and muscular cramps. If use of the drug is not discontinued, the child soon becomes pale out of proportion to the anemia. There is loss of weight, the skin and mucous membranes become dry and weakness and irritability develop. At times the temperature is elevated. Finally, stupor and deep breathing occur.

"The most important group of symptoms is related to disturbances of renal function, notably the appearance of calcium in abnormal amounts and of calcium-containing casts in the urine, albuminuria and finally fixation of the specific gravity at low levels, together with signs of renal insufficiency. An early sign of danger is a persistently positive result of the Sulkowitch test." The unfavorable prognosis of high blood pressure and of a high blood urea nitrogen level has been emphasized.

"There is frequently a low erythrocyte count. The serum calcium is usually high, ranging between 12 and 21 mg. per hundred cubic centimeters. With uremia, the blood urea, sulfate, creatinine and phosphorus levels are elevated and the calcium levels decreased.

"Roentgenograms may show bony atrophy and destruction from hypervitaminosis D. Calcium deposits may be seen in the kidneys, bronchi and alveoli, gastric mucous membranes, blood vessels and periarticular tissues."

Calcium deposits have been described in the superficial layers of the periphery of the cornea, most marked at the palpebral fissures (band keratitis). "These may be seen under direct vision without magnification in patients with prolonged hypercalcemia. Biomicroscopy also may reveal crystalline calcium deposits in the deep conjunctivas of the palpebral fissure in patients with chronic hypercalcemia."

"Early hypervitaminosis D usually raises the serum calcium level. . . . In hyperparathyroidism with definite changes in the bone the serum alkaline phosphatase is elevated. The absence of this finding in hypervitaminosis D may be a helpful diagnostic point. . . . Intoxication from the administration of massive doses of vitamin D is more widespread than the reports in the literature would appear to indicate, for it may masquerade as renal disease. . . . The history of massive ingestion of vitamin D is most important in the differential diagnosis."

Infection of the Newborn and Aureomycin — Ribadeau-Dumas, L., Héraux, Debray, J. and Verliac — *La presse médicale*, 58: 921 (August 26) 1950.

Among the causes of infection in the newborn, an important place should be reserved for infections which precede delivery. Many well known investigations have shown that bacteria can pass through the placenta. However, some authors have considered that passage through the placenta is possible only in the cases of prolonged or very virulent disease capable of altering the structure of the placenta. It is also known that soluble toxins can reach the placenta. However, many contradictory facts exist, for example, those which concern the Rh factor, according to which it seems to be very difficult to define exactly the laws which govern the transplacental passage of various substances or particles circulating in the maternal blood.

The bacteria of the vagina and vulva are the ones which usually intervene in infections of the newborn. This flora is extremely variable and is kept in check by bactericidal substances, especially the acidity of the media due to the presence of the *B. acidophilus* of Döderlein. There are certainly other factors such as the estrogens and vitamin B_2. According to one writer there is an interdependence between the vaginal flora, and the *p*H and the blood estrogen level. The development of the contaminating flora is rendered possible by a hypofunction of the ovary. Hence it is necessary to develop an autodefense, the most simple test of which is the degree of the *p*H. It cannot be expected to reach a sufficient value in all cases.

Bacterial invasions of vaginal origin usually occur after delivery and reach the fundus of the uterus at about the third day but the ascension of the bacteria may begin during labor and before rupture of the membranes. The cause which favors the aggression of the bacteria is above all the duration of labor after rupture of the membranes. In such cases contact of the fetus with septic fluids is very easy and infection becomes possible. These ideas are of great importance because they permit an understanding of the old epidemics of maternal septicemia. They also explain infections of the newborn, the etiology of which is obscure.

In fact, the point of origin of an infection of the newborn is far from always being evident. According to several writers a lesion of the umbilicus may pass unnoticed even if it is possible to follow the streptococcus, staphylococcus or pneumococcus from the thrombosed clots of the umbilical vessels through the liver into the lungs.

Another considers that infection of the newborn is usually due to the colon bacillus which has a predilection for premature infants. The penetration of the bacteria occurs at various times, aspiration of an infected amniotic fluid during delivery or deglutition of maternal secretions during passage through the vagina or vulva.

It can be admitted that the digestive tract is aseptic at birth and for a period of 3 to 20 hours but bacteria which the fetus has acquired from the maternal genital passages can be found in the meconium in a few hours. It has been found that while the meconium may seem to be sterile there may be found many bacteria in histologic sections of the wall of the stomach or small intestine.

During the course of delivery, under the influence of anoxia, the infant may have made several inspirations and there may be found in the lungs amniotic debris, vernix caseosa, particles of meconium and sometimes dense masses of bacteria so that to the dangers of obstruction there may be added those of broncho-alveolitis.

The role of cerebromeningeal hemorrhage must also be taken into consideration as it is also the result of anoxemia. There is in the semeiology of infection of the newborn a certain complexity due to the

participation of a still imperfectly formed nervous system the lesions of which falsify all the reactions which could be expected to be found against any harmful agent in a normal organism. An infant which is born in a state of apparent death can sometimes be reanimated by simple deobstruction but atelectasis may still persist and about the third or fourth day there may be attacks of apnea with grave disorders of the general condition. On lumbar puncture there may be obtained a clear, pink or yellow fluid under hypertension and the condition of the infant may improve after the puncture. However, these first complications may be followed by disorders of growth due to the infection and favored by irritation of the nervous system. The signs of this may appear at variable times. They may be immediate, the child is born with a bronchopneumonia in cases of premature rupture of the membranes. But there are cases in which there was no difficulty during labor, the mother was apparently normal and yet the infant died on the second day from purulent pleurisy. In general, the infection becomes manifest after a variable period of incubation. When an autopsy is made amniotic debris is generally found in the alveoli. There are also cases in which a cerebromeningeal hemorrhage at the onset is followed by vomiting, these cases may be due to a possible septic aspiration. A chemical pneumonia of prematures has been described in which droplets of fat from regurgitated milk were found in the pulmonary parenchyma.

There is an indefinite syndrome characterized by loss of weight, disorders of thermal regulation and digestive disorders. The most constant sign is the loss of weight and when nothing can be found to explain it a hidden infection should be suspected. A careful examination of the pharynx, a radiologic examination of the lungs or an analysis of the urine may show a previously unsuspected localization but often no cause can be found.

A wide use of sulfonamides has reduced infant mortality due to infection but such treatment must be given early because its efficacy depends on the time which its action enters into play. However, after an apparently successful result for a few days, sulfonamides, streptomycin or penicillin are incapable of arresting the course of the disease and there is a terminal marasmus. These inconstant results have led to the use of aureomycin and the results obtained have exceeded all expectations. The author used aureomycin in 13 cases which can be divided into three groups.

The first group included 4 patients. On the second to sixth day there was a loss of weight which could not be explained. Penicillin failed but aureomycin produced an immediate cure with a remarkable increase in weight.

The second group included 5 cases where the examination showed an early or late otitis. The loss of weight was immediate or began on the fourth to eighth day. It preceded the appearance of an otitis and paracentesis was performed. Penicillin and streptomycin failed but treatment with aureomycin gave excellent results.

The third group included 4 cases in which there were cerebromeningeal hemorrhages with an infection. All of these patients had a late serous otitis. The clinical course evolved in two stages. The early disorders were calmed by a lumbar puncture which resulted in a clear, pink or yellow fluid under hypertension. Improvement seemed evident but there was a loss in weight a few days later. Penicillin gave only transitory or negative results up to the time that aureomycin was given. In 1 case biotics were used at first without any result but on the forty-fourth day aureomycin was administered and the infant recovered. Aureomycin seemed to fail in 1 case but this patient did not have any infection. There was a grave disorder of thermal regulation due to a large cerebromeningeal hemorrhage extending into the ventricles.

Rather large doses of aureomycin were given, 0.25 daily. However, this dose was reduced by regurgitation or vomiting so later small doses were given six times daily. The duration of treatment was four days on an average and never exceeded one week. There were no signs of intolerance. However, attention should be called to a few curious facts. During treatment with aureomycin there sometimes was a serous otitis which was benign or some disorders of deglutition or of the pharynx or larynx. Perhaps these complications were due to a focal reaction.

Thus aureomycin produced results in these cases which could not be obtained with other biotics. Undoubtedly there are many cases in which sulfonamides, penicillin and streptomycin have given good results in infected infants but the present cases show that aureomycin may be very effective when other methods fail.

Nephrito-Nephrosis as a Sequel During the Course of a Toxicosis and Secondarily Fatal — BERTOYE, P., MONNET, P. AND DEPIERRE, A. — *Pediatrie*, 39: 636, 1950.

The patient was a boy 3½ months old. He weighed about 10 pounds at birth. He was breast fed for a month and then artificial feeding was given. The diet was well supported at first and then digestive disorders appeared. Locust bean starch gave temporary relief at first but later he became worse and was sent to the hospital.

On admission, on May 22, his temperature was normal but he had diarrhea, great dehydration, his eyes were sunken and he weighed about 9½ pounds. No examination was made of the urine at that time. The ordinary treatment did not have any effect and on the next day he was given a transfusion of 400 cc. of preserved blood. His condition then changed rapidly and he gained weight.

On May 31, nine days after admission, he had a fever of 101.3° F. and a systematic paracentesis showed a seropurulent discharge on the left side and pus on the right side.

On June 6, there was edema, especially of the face. An examination of the urine showed 1 Gm. of albumin per liter. From this time and until death six months later there was generalized anasarca with edema, abdominal meteorism and possibly ascites.

Various forms of treatment were tried, theobromine, albuminous diet with thyroid extract and small transfusions. Improvement was noted each time the treatment was changed but it did not continue. The edema evolved in successive attacks and he became cachectic.

The albumin in the urine increased to 15 Gm. per liter. The urine contained some red cells and many hyaline and granular casts. The blood contained 0.20 urea, 3.50 cholesterol, 13.50 lipids, 29.75 total proteins, 18.6 serine and 11.80 globulin. The Wassermann reaction was negative. The cutaneous test for tuberculosis was negative. A pulmonary radiograph did not show anything abnormal.

The child died in a state of marasmus at the end of six months.

Autopsy.—The kidneys were large, lobular and pale. The structure of the pyramids was apparently conserved. Decapsulation was easy. The liver was congested. The lungs were congested and there were foci of bronchoalveolitis. The spleen was normal.

The histologic examination showed that the liver and spleen were normal. There were no alterations of the glomeruli of the kidney. Some tubules contained hyaline and hematic casts. Hence there was a nephrosis histologically.

Hence after a toxic state in a nursling who had received 400 cc. of preserved blood, there developed an edematous nephropathy of the nephrotic type which had secondarily resulted in death. The blood transfusion had apparently played an important role in the retrogression of the toxic state and it did not seem to be the cause of the renal lesions as it was well supported.

The frequent reaction of toxicoses on the kidney is well known. Albuminuria and casts are the most common findings but these phenomena are the result of a purely functional involvement and are not usually followed by an evident nephropathy. That this possibility may occur is the reason for presenting this case.

Immune Responses and Reactions to Diphtheria and Tetanus Toxoids, with Pertussis Vaccine, Aluminum Phosphate Precipitated — MCCOMB, JAMES A. AND TRAFTON, MARION Z. — *New England Journal of Medicine*, 243: 442 (September 21) 1950.

"Reactions in a clinical study of diphtheria and tetanus toxoid with pertussis vaccine, aluminum phosphate precipitated, are tabulated."

"The circular accompanying each vial advised three intramuscular injections of 0.5 cc. each at four week intervals. As only one 'antigenic cyst' occurred after injection, it is believed that for the most

Table 1. Reactions.

Injection	Total No. of Injections	Percentage with Local Reactions							
		Erythema				Infiltration			
		0	2.5 cm.	2.5-5 cm.	5 cm.	0	2.5 cm.	2.5-5 cm.	5 cm.
First (0.5 cc.).....	113	45	30	20	5	80	11	6	3
Second (0.5 cc.).....	87	42	30	20	8	79	12	6	3
Third (0.5 cc.).....	87	53	27	14	6	79	17	1	3
Booster (0.3-0.5 cc.)	134	57	13	13	17	72	16	6	6

Table 1. (Concluded).

Injection	Percentage with Fever			Percentage with Other Reactions		
	None	Slight*	High†	Irritability	Vomiting	Anorexia
First (0.5 cc.).....	91	8	1	8	1‡	—
Second (0.5 cc.).....	88	10	2	13	1	—
Third (0.5 cc.).....	86	9	5	7	2	—
Booster (0.3-0.5 cc.)...	93	4	3	7	—	2

*100-102°F.
†102-104°F.
‡1 cyst.

part this instruction was followed." The importance of intramuscular injection has been stressed by many and recently emphasized by one writer, whose recommendations are as follows:

"Alternate lateral gluteal areas (starting with the left proximal area) are preferred sites for the administration of alum precipitated antigens in children under 3 years of age. Needles (12 mm., 25 gauge) and syringe (1 cc.) are cleansed in distilled water, dried and sterilized in an oven at 160° C. for one hour. The child is held firmly to prevent squirming. The needle does not deviate from its original course. Each deeply administered dose is terminated with 0.1 cc. of air. The needle remains in place for a few seconds before it is quickly withdrawn. The site is immediately massaged gently with sterile gauze. Subsequent doses are never administered near the site of a previous injection. Occasionally a deep circumscribed nodule may be palpated for a month or longer, but abscess has been almost completely eliminated."

Children with a tendency to convulsions should be omitted from any immunization against pertussis.

"Reactions were reported on forms provided. . . . In a total of 765 injections 583 children were recorded as having no erythema and 708 as having no infiltration.

"In an effort to assess more accurately the incidence and degree of local and general reactions the reports of patients of private physicians and the smaller clinics were separated and summarized (table 1). In these reports the mother for the most part indicated the reactions or lack of them. The details on most cards showed careful observations.

"In age distribution 40 per cent of the children receiving injections shown in table 1 fell in the group of 6 to 12 months, and 23 per cent were 4 years and older." The highest percentage of larger local reactions was found in the "booster group."

"Only 49 blood samples were obtained from private patients and clinics. A total of 76 samples were obtained, including 27 from children in institutions who for the

Table 2. Titration of Pertussis Serum Agglutinins One Month After Immunization.

Agglutinin Titers	Patients Under Two Yr.	Patients Over Two Yr.	Total Patients in Both Age Groups
<1:160	0	3	3
1:160	7	9	16
Total without protective titer	7 (15.5%)	12 (38.7%)	19 (25%)
1:320	12	9	21
1:640	13	7	20
1:1280	8	2	10
1:2560	5	1	6
Total with protective titer	38 (84.5%)	19 (61.3%)	57 (75%)

most part were between 2 and 5 years of age. Approximately 65 per cent of the children from whom bloods were obtained were under 1 year of age at the time of the first injection.

"The results of the tetanus antitoxin titrations showed 100 per cent immunity with 0.1 unit per cc. as the level indicating immunity. Small amounts of blood in 5 samples reduced the number of tests that could be completed to 71.

"Diphtheria antitoxin titrations similarly showed 100 per cent immunity with 0.03 units per cc. as the level most commonly considered adequate."

Table 2 demonstrates the immunity to pertussis as judged by agglutination titers of 1:320 or over. The writers do not have an explanation for the poorer results in the older children. "The group of children 2 years of age and under is considered the more important from the standpoint of complications from the disease. . . . The figures for diphtheria and pertussis immunity are not presented as an accurate measure of the antigenic efficiency of the triple antigen used in this study because of the lack of preinjection blood titers."

Symposium Section

Subclinical Poliomyelitis

We can recall a time, not so long ago, when viruses were considered weak, if not totally ineffective, antigens. That was when they were among the unknowns and their existence was demonstrable only because some vague substance passed through a Berkefeld filter from a suspension of material obtained from a patient with what was believed to be an infectious disease of obscure etiology. The infectious nature of this substance could be confirmed by its being capable of producing a disease in one or more experimental animals. The usefulness of this procedure was in that it enabled investigators to reproduce diseases which simulated the malady in the humans from whom the filtered material had been obtained. So the substances were called filtrable viruses.

One of the earliest examples of the use of this procedure in which we are especially interested here was in 1909 when Landsteiner and Popper[1] discovered that poliomyelitis could be transmitted to rhesus monkeys by inoculating them intraperitoneally with such a filtrate from material obtained from active cases in humans. Shortly after, in the same year, Flexner and Lewis[2] were able to show that the disease could be transmitted indefinitely from animal to animal, and for many years the maintenance of these filtrates or viruses, as they are now known, depended solely on such animal transmission. Animals were expensive and the technic was laborious and too often disappointing. So the study of the viruses progressed slowly.

Then came the discovery that viruses could be grown on fertile eggs of hens provided they were incubated for varying periods. It was found that if suspected filtrates were injected into the developing chicken embryo according to the technic now so widely known, it could be grown and transplanted to other eggs in varying stages of incubation just as we now so routinely do on other media with microscopically recognizable bacteria. So with the discovery of egg media and, shortly after, the electron microscope, the investigation of viruses is not so handicapped as formerly. Moreover, as this is written eggs are still cheaper than monkeys. It is still necessary however, to use mice in the study of some viruses.

One observation that has been made, which refutes the conception that viruses are poor antigens, is that some animals and humans may acquire immunity in varying degrees by subclinical infection during epidemics or casual exposure during endemic periods, just as they do to other infections. This individual resistance is due to variations which depend on many factors. The most common of these, which first occurs to all of us, is the widely accepted opinion that viruses like other organisms possess varying degrees of attenuation and virulence. Second, but equally important, is the "host factor" which determines the form which infections of any kind may take in human beings. This behavior of the viruses which have been associated with poliomyelitis has been a fascinating study, out of which has come a growing amount of evidence that certain forms of minor illness which are perplexing may be associated with or occur during outbreaks of poliomyelitis. They have also been known to occur when poliomyelitis is not prevalent, even though in some instances, as will be discussed, poliomyelitic virus may be obtained from patients with these minor conditions.

To illustrate we may start with a recent report from the Chicago Health Department and the Baptist Hospital of Birmingham, Alabama, which discusses the incidence of what is called "subclinical poliomyelitis" in an urban area according to age groups. This report is abstracted

1. Landsteiner, K. and Popper, E.: *Ztschr. f. Immun. u. exper. Therap.*, **2**:377, 1909.
2. Flexner, S. and Lewis, P. A.: *J. A. M. A.*, **53**: 1639, 1909.

elsewhere.* It is an additional contribution to a subject which has interested others in recent years and consequently gives us a "peg" upon which to hang an editorial review which seems especially appropriate after another big "polio" year. Casey, Fishbein, Schabel and Smith,[3] the authors of this latest contribution, trace the recognition of what they have called subclinical poliomyelitis to Wickman,[4] who reported such minor illnesses among contacts of paralytic poliomyelitis 47 years ago. It was again emphasized by the eminent student and teacher of epidemiology, Wade Hampton Frost, of the Department of Epidemiology at the Johns Hopkins School of Hygiene and Public Health, in 1913. Dr. Frost considered that "the paralytic case may perhaps be a complication or accident in the course of poliomyelitis; that the disease occurs throughout the world in endemic form, particularly in large cities; that the population of cities becomes immunized by subclinical infection early in life, usually before 5 years of age (since older children and adults are less frequently attacked); that the disease has a seasonable distribution of enteric and insect-borne diseases, but that it is transmitted largely by person-to-person contact." This, for the most part, is the conception which prevails at the present time and closely simulates what occurred in the epidemic of measles as observed in the Faroe Islands by Peter Ludwig Panum, the young Dane, whose extraordinarily thorough observations 107 years ago are still used as a basis of the epidemiology even until now. Those who may recall that every year Dr. Frost used to lecture on this epoch-making work of Panum before his graduate students at Johns Hopkins School of Hygiene and Public Health fully appreciate the extent of Panum's influence[5] in shaping his opinion on the epidemiology of infectious diseases as a whole.

Casey and his associates[3] adduce much more of the earlier evidence to support the incidence of what they have called subclinical poliomyelitis which, according to Stocks, the well known British epidemiologic statistician, may be estimated upward of 100 cases to each paralytic case of poliomyelitis in endemic areas.

In recent years many others, whose observations are not included in the report of Casey and his associates, have been interested in minor illnesses which seem to be associated with poliomyelitis. It may be appropriate first to recall that it has long been appreciated that most viruses are under some circumstances neurotropic. It is for that reason they so often cause neurologic complications or sequelae in viral-borne diseases; notable examples are measles, German measles, smallpox, chickenpox, vaccinia, antirabic treatments and others. In addition, convincing evidence has accumulated to indicate that many bizarre and, consequently, perplexing neurologic symptoms may follow these viral diseases or they may be initiated independently. Of course, all of these puzzling maladies associated with viruses had their beginning following the 1918 pandemic of influenza, as it was called, when we first talked and wrote about "lethargic encephalitis." Later when the affinity, which most if not all viruses possess, for nerve tissue became more widely recognized, we began to be conscious of the wide variety of conditions which Hammon and his associates[6, 7] have called the "virus encephalitides."

But here we are more concerned with those minor illnesses which are associated with poliomyelitis in one way or another.

* See page 349.

3. Casey, A. E., Fishbein, W. I., Schabel, F. M., Jr. and Smith, H. T.: Incidence of Subclinical Poliomyelitis in an Urban Area According to Age Groups, *Am. J. Pub. Health*, **40**: 1241 (October) 1950.
4. Wickman, I.: *Beitrage zur Kenntnis der Heine-Medinschen Krankheit.* Berlin: S. Karger, 1907. Cited by 3.
5. Panum's report originally published in the *Bibliot. f. laeger.* (Copenhagen) 3R, **1**: 270, 1847 and consequently not generally available, it was restricted to authors or readers familiar with the Danish language or had translations. Dr. Frost was so impressed with the work of the young Panum that a translation was made for him by Ada Somerville Hatcher during his tenure as Professor of Epidemiology at Johns Hopkins School of Hygiene and Public Health. It was later revised and edited by her and Dr. James Angus Doull, Dr. Frost's former associate. This translation was then published under the sponsorship of the Delta Omega Society, an honorary public health society, in accord with its policies to foster the republication of public health classics that are not generally available to students of public health. It is distributed by the American Public Health Association, 1790 Broadway at 58th Street, New York 19, New York through its Book Service. It should be in the library of all interested in the epidemiology of communicable diseases.
6. Hammon, W. M. and Reeves, W. C.: Recent Advances in the Epidemiology of the Arthropod-Borne Virus Encephalitides, *Am. J. Pub. Health*, **35**: 994 (October) 1945.
7. Editorial: Virus Encephalitides, *Internat. M. Digest*, **49**: 56 (July) 1946.

In addition to "subclinical poliomyelitis," a title which we have selected as most descriptive, these illnesses have been called abortive polio, summer grippe, summer disease, three day fever, aseptic meningitis and, finally, Coxsackie disease. This brings us to the origin of the last name which in a large measure aroused interest in the whole subject which we are endeavoring to present.

This last name for these illnesses originated when a virus was isolated from 2 cases of clinical poliomyelitis in upstate New York by Dalldorf and his associates [8, 9] of the Division of Laboratories and Research of the New York Department of Health. This virus was recovered by Dalldorf and Sickles during several small epidemics of poliomyelitis and was named after the small village of Coxsackie which is located 20 miles south of Albany, but on the west bank of the Hudson river. The name has stuck and it has been isolated in localities far removed from this little village. For example, Findlay and Howard[10, 11] in a report from England, have just suggested that it may be the cause of Bornholm disease (epidemic diaphragmatic pleurodynia). A short while after the discovery of the New York group, Melnick and his associates[12] of the Section of Preventive Medicine and Department of Pediatrics of Yale University School of Medicine isolated a virus from patients diagnosed as nonparalytic poliomyelitis or aseptic meningitis, which they considered similar to the Coxsackie virus. This filtrable virus was obtained from the feces during an illness resembling nonparalytic poliomyelitis which occurred during 1948 in southern New England. Similar cases of this nonparalytic poliomyelitis had also been noted in the previous year in the New England area. It had also been reported before in Louisiana, [13, 14] Tennessee,[15] Ohio,[16] Rhode Island, [17] Connecticut[18] and in many other states according to unreported communications to some of those who have written about such cases. All these illnesses have been connected with either the Coxsackie viruses or some of the other viruses associated with poliomyelitis.

In Louisiana, Webb, Wolfe and Simpson,[13] and Webb, Wolfe and Howitt[14] reported an outbreak of a disease in Shreveport, Louisiana, characterized by high fever, intense headache and brief duration. It did not fit into any of the known categories of illness. The fever was initiated abruptly, ranged from 101° to 104° F. and the duration was three days in 60 per cent of the patients. Throat washings or repeated swabbings were placed in a special culture medium, quick frozen and submitted by air mail to the Virus Laboratory of the United States Public Health Service in Montgomery, Alabama. Stool and blood samples taken during the acute stage and convalescent blood samples were also submitted. A filtrable virus isolated from throat washings of 1 child and stool of another was fatal for mice and hamsters 3 to 7 days old, producing severe myositis. Blood serums from 5 children tested gave definite protection against one of the strains. Both strains were shown to be identical with type 2 of the Coxsackie virus of Dalldorf and Sickles.[8] Because of the consistent duration of the fever in 60 per cent of the patients, Webb and his associates called the acute illness they observed during the summers of 1947 and 1948 in 86 children, "three day fever."

8. Dalldorf, G. and Sickles, G. M.: An Unidentified, Filtrable Agent Isolated from the Feces of Children with Paralysis, *Science*, **108**: 61 (July 16) 1948.
9. Dalldorf, G., Sickles, G. M., Plager, H. and Gifford, R.: A Virus Recovered from the Feces of "Poliomyelitis" Patients Pathogenic for Suckling Mice, *J. Exper. Med.*, **89**: 567 (June 1) 1949.
10. Findlay, G. M. and Howard, E. M.: Coxsackie Viruses and Bornholm Disease, *Brit. M. J.*, **1**: 1233 (May 27) 1950.
11. Editorial: Bornholm Disease and Coxsackie Virus, *Internat. M. Digest*, **57**: 120 (August) 1950.
12. Melnick, J. L., Shaw, E. W. and Curnen, E. C.: A Virus Isolated from Patients Diagnosed as Nonparalytic Poliomyelitis or Aseptic Meningitis, *Proc. Soc. Exper. Biol. & Med.*, **71**: 344 (July) 1949.
13. Webb, C. H., Wolfe, S. G. and Simpson, V.: Clinical Features of a Summer Disease (Three-Day Fever), Apparently of Virus Etiology, *New Orleans M. & S. J.*, **101**: 249 (December) 1948.
14. Webb, C. H. and Wolfe, S. G. (with Virus Laboratory Studies and Isolation of Coxsackie Virus by Beatrice F. Howitt, M. A., Montgomery, Ala.): "Three Day Fever," *Am. J. Dis. Child.*, **80**: 245 (August) 1950.
15. Humbert, W. C., Tucker, C. B., Mosley, K. T. and Bishop, L. K.: An Epidemic of Acute Meningo-Encephalitis in Giles County, Tennessee; Unusual Disease, *Am. J. Pub. Health*, **37**: 564 (May) 1947.
16. Sabin, A. B. and Steigman, A. J.: Poliomyelitis Virus of Low Virulence in Patients with Epidemic "Summer Grippe or Sore Throat," *Am. J. Hyg.*, **49**: 176 (March) 1949.
17. Jaworski, A. A. and West, E. J.: Aseptic Meningitis of New Virus Origin, *J. A. M. A.*, **141**: 902 (November 26) 1949.
18. Curnen, E. C., Shaw, E. W. and Melnick, J. L.: Disease Resembling Nonparalytic Poliomyelitis Associated with a Virus Pathogenic for Infant Mice, *J. A. M. A.*, **141**: 894 (November 26) 1949.

Another striking and equally perplexing report was that of Sabin and Steigman[16] on which we have previously[19] commented in these columns. This was an outbreak of an illness in Cincinnati and its surrounding area, which for the want of a better name or specific diagnosis came to be known as "summer sore throat" or "summer grippe." Like the outbreak reported by Webb and associates, this disease was mild and the patients usually got well after three to seven days. None were hospitalized; the cases were not reported to the health department, so no actual incidence of the disease could be estimated. Sabin and Steigman roughly assumed that it was as high as 10,000 cases.

The onset of this summer grippe was not unlike that reported by other authors. It was usually sudden with fever, headache, nausea or vomiting or both, vague epigastric distress or generalized abdominal pain, sore throat, generalized aching or soreness of the muscles and joints. As a rule there was no diarrhea, no rhinitis with inflamed nasal mucosa, no evidence of laryngotracheobronchial irritation with cough, although a few patients with upper respiratory symptoms were occasionally seen. These patients were rarely visited by their physicians more than once, and many were not seen at all.

The cases of Dalldorf and associates, from which 136 fecal specimens were collected and from which the Coxsackie viruses were isolated, not only followed the sequence described by Webb and associates and Sabin and Steigman but they were a little more severe. In a later communication Dalldorf[20] adds that some were hard to distinguish from poliomyelitis. Some had spinal rigidity and 1 case was frankly paralyzed and left the hospital a month following admission in a wheel chair. Five others had transient weakness of arm, leg or back muscles. Dalldorf's group examined the cerebrospinal fluid in 7 cases and all showed an increased number of cells. In 3, the total count amounted to 200 to 250 cells per cu. mm. Webb and Wolfe, who mention stiffness of neck and back as symptoms, did spinal punctures in 3 cases and report "evidence of meningoencephalitis" in 3 patients. However, it should be recalled that in the series of Webb and Wolfe and Sabin and Steigman the malady was so mild that the patients too often recovered before extensive study was possible.

There have been a few more less consequential reports of ill defined and bewildering mild diseases either associated with poliomyelitis or which were believed to have some connection. After all, we cannot disregard the fact that viruses are still as elusive and puzzling as when we knew them as vague substances so fine and ultramicroscopic that they passed through Berkefeld's filter; when we could maintain their existence only by transmitting them from animal to animal; when they were vague, enigmatic and beyond the limits of existing microscopes, and when we realized their existence only because we could produce a disease in one or more experimental animals with the unknown substance that passed through the filter from a suspension of material obtained from an infected human or animal.

Of course that has changed since we can now grow the mystifying substance that passes through improvements of the older Berkefeld filter, on partially incubated fertile eggs of the barnyard hen and we can see what we have grown in the electron microscope, we have rapidly developed means of detecting its strains, we can measure its antigenicity, the antibody response in animals and subject it to other laboratory procedures which are being developed in well equipped and staffed laboratories created for the exclusive study of the elusive viruses. The outlook is more hopeful every day.

Certainly there is no reason at all for discouragement, even though none other than the eminent Karl Meyer of the George Williams Hooper Foundation of the University of California, which has sponsored many viral studies, expressed very frankly, certainly very clearly and bluntly, what may have been and still may be in the minds of many, when he said[21] that, "the present day information (1947) on viral

19. Editorial: Epidemic "Summer Grippe" and Poliomyelitis, *Internat. M. Digest*, **55**: 122 (August) 1949.
20. Dalldorf, G.: Suggested Studies of Poliomyelitis, *New York State J. Med.*, **49**: 1330 (June 1) 1949.
21. Meyer, K. F. and Eddie, B.: The Knowledge of Human Virus Infections of Animal Origin, *J. A. M. A.*, **133**: 822 (March 22) 1947.

agents is in a state of flux; changes in fact and in point of view occur in kaleidoscopic fashion, and there is considerable hesitancy to make final conclusions." Some progress has been made but the study of viruses has a long way to go before we can know the habits of and classify the weird little glistening balls and bizarre Picasso designs we see in the electron microscope. They are there and we know that they are the ultramagnification of what we have grown in the tissue of the chicken embryo from material which has passed through a Seitz filter. After all, that is traveling a long way. We have at least arrived at, and may have passed, the point which Louis Pasteur and Antonj van Leeuwenhoek reached at the dawn of bacteriology and microscopy. Diligent and painstaking work of those we have herein cited deserve nothing but praise and encouragement. Progress is what will come from their efforts. More power to them.

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Cigarettes and Cancer

The steady increase in the recorded deaths from cancer of the lung is startling. The trend is the same in all countries where Western civilization is predominant, except apparently in Iceland. There can be little doubt that the incidence of cancer of the lung is really increasing, and tarred roads, exhaust gases, common respiratory infections, certain types of occupation and tobacco smoking have all been blamed for the greater frequency of the disease. Of these possible causes smoking seems the most likely, for the rise in the death rate from cancer of the lung has followed a great increase in the consumption of tobacco and cigarettes. Several groups of workers have undertaken investigations to prove or disprove the suggested association. It is not easy to adopt an unbiased attitude to the concept that smoking may cause cancer. We are all either smokers or nonsmokers and each group may regard the other as prejudiced.

Those who smoke more than 40 cigarettes a day, allowing 10 minutes per cigarette, are occupied with smoking for about 6½ hours. There are no days off, and therefore the heavy smoker smokes for about 46 hours a week. This almost amounts to an occupation. Moreover, smokers heavily outnumber nonsmokers, and this complicates statistical considerations. Even so, the proof that cancer of the lung is associated with smoking must obviously be based on statistical and not on clinical evidence.

The ideal investigation would be to compare the incidence of lung cancer in a population exclusively composed of nonsmokers with that in populations composed of smokers of various grades, from very light to excessive.

Recently Wynder and Graham[1] studied 684 cases of bronchiogenic carcinoma, 634 of the patients having been personally interviewed. They found that the nonsmokers among male patients with cancer of the lung amounted to 1.3 per cent of the total, compared with 14.6 per cent of nonsmokers among men in the general hospital population without cancer. Whereas only 19.1 per cent of men in the latter were classified as "excessive and chain-smokers" as many as 51.2 per cent of the patients with cancer came into this category.

In another report from Iceland Dungal[2] has drawn attention to the comparative rarity of lung cancer in that island. His study is based on the records of 1,939 necropsies performed in Reykjavik from 1932 to 1948. There were 417 malignant growths in their series and 12 cases of primary lung carcinoma. This is a very much smaller proportion than is found in other comparable communities. Dungal points out that smoking, and particularly cigarette smoking, has only recently become popular in Iceland on a scale at all resembling that in most European countries. In 1945 the consumption of tobacco per head in Iceland reached 1 pound per annum.

There is a shortage of convincing experimental evidence about tobacco as a cause of cancer. Animals subjected to an atmosphere of smoke from mechanically smoked tobacco can be compared, not with smokers, but with nonsmokers in a smoking compartment. It has never been proved experimentally that carcinogens are formed during the smoking of tobacco, though this would not be surprising in the light of the probable results of destructive distillation of any organic matter under conditions of restricted oxygenation.

1. Wynder, E. L. and Graham, E. A.: Tobacco Smoking as a Possible Etiologic Factor in Bronchiogenic Carcinoma, *J. A. M. A.*, **143**:329 (May 27) 1950. Extensive bibliography appended.
2. Dungal, N.: Lung Carcinoma in Iceland, *Lancet*, **2**:245 (August 12) 1950.

The practical question which the doctor in practice has to answer is whether any of his patients—for instance, those with smoker's cough—should be advised to give up smoking.

There is no evidence about the degree of risk which cigarette smokers take, but it does apparently increase in direct proportion to the amount smoked daily and to the total duration of the habit.

The Treatment of Poliomyelitis

Stimson[1] draws attention to many uncertainties over the best methods of treating acute poliomyelitis. He considers the possible dangers of transporting patients long distances for admission to hospital, and refers to some observations suggesting that long journeys in the early stages of the illness induce more severe paralysis. He points out that it is also uncertain (1) whether lumbar puncture should be carried out in all cases, (2) whether the patient should be hydrated or dehydrated, (3) what is the proper use of sedatives, (4) whether muscle-relaxing drugs should be administered, (5) what is the right treatment for urinary retention, and (6) what is the proper use of postural drainage and tracheotomy.

Certainly it is not always easy to get scientific guidance on what should be done. It is now widely held[2] that complete rest and muscular relaxation in the preparalytic stage increase the resistance of the spinal cord cells; and we must, therefore, bear in mind the possible harm done by long anxious consultations, exhausting physical examinations, lumbar punctures and removal to hospital. It is essential, of course, to exclude meningitis, for this requires immediate specific treatment; but once this has been excluded, perhaps the less done in the preparalytic stage the better, apart from ensuring that the patient gets plenty of sleep. As regards treatment in the chronic stage of the disease, too, there are many different opinions, and reliable observations on the value of various methods of physiotherapy are strikingly few. In short, the present position leaves much to be desired, and there is a need for special effort by research workers who have a good knowledge of the physiology of spinal cord, nerve cell and muscle. Bourdillon et al.,[3] have been applying modern physiologic knowledge to the study of cases treated in mechanical respirators, and this is a useful step in the right direction.

1. Stimson, P. H.: Some Debated Points in the Treatment of Acute Poliomyelitis, *J. Pediat.*, **36**:704 (June) 1950.
2. Horstmann, D. M.: Acute Poliomyelitis, Relation of Physical Activity at the Time of Onset to the Course of the Disease, *J. A. M. A.*, **142**:236 (January 28) 1950; Russell, W. R.: Poliomyelitis: the Preparalytic Stage, and the Effect of Physical Activity on the Severity of Paralysis, *Brit. M. J.*, **2**:1023 (December 27) 1947; *ibid.*, Paralytic Poliomyelitis: the Early Symptoms and the Effect of Physical Activity on the Course of the Disease, *ibid.*, **1**:465 (March 19) 1949.
3. Bourdillon, R. B., Davies-Jones, E., Stott, F. D. and Taylor, L. M.: Respiratory Studies in Paralytic Poliomyelitis, *Brit. M. J.*, **2**:539 (September 2) 1950.

Prostigmine in the Treatment of Pyrosis of Pregnancy

Dumont and Bourbon[1] record the results of prostigmine therapy in 46 cases of pyrosis in pregnancy. The drug was given in 4 cases by intramuscular injection in dosage of 0.5 mg., and in the remainder by mouth in dosage varying from 15 to 75 mg. In the first group the treatment was successful in 2 cases; in the second group the symptoms were successfully combated in 20 cases, improved in 5; the remainder failed to respond to treatment. In the oral group, 12 patients were treated with dosage of 30 mg. with 8 successes and 2 improved. In 19 cases the rapidity and duration of action were observed; the rapidity of action varied from five minutes to one hour and the duration of action from one hour to two days. Of the 46 cases treated, complete success was obtained in 48 per cent, amelioration in 15 per cent, failure in 37 per cent. The drug was well tolerated by all patients and had no untoward effect on the normal course of the pregnancies.

1. Dumont, M. and Bourbon, P.: Prostigmine in the Treatment of Pyrosis of Pregnancy, *La presse médicale*, **58**:646 (June 10) 1950.

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